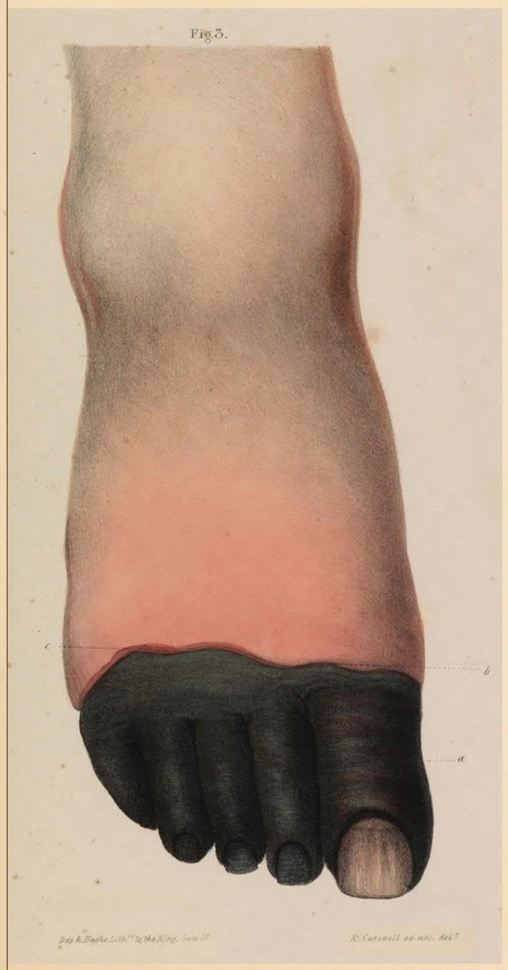
# HYPERCOAGULABLE DISORDERS – IMPLICATIONS FOR WOUNDS & SURGERY

## PATHOPHYSIOLOGY, CLINICAL FEATURES, DIAGNOSIS & TREATMENT

AND

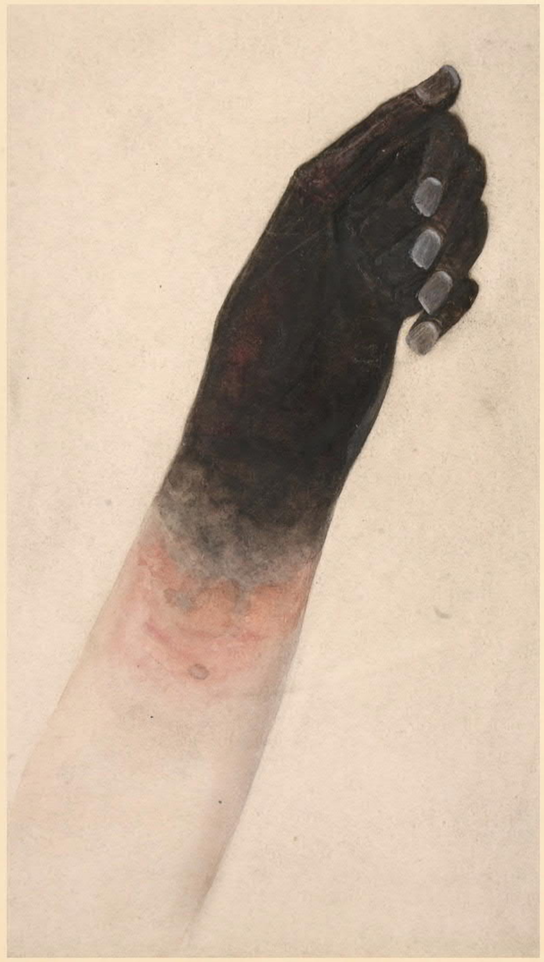
Insights About the Historical Understanding of this Subject and Why These Problems Remain Perpetually Under Appreciated, Under Recognized, and Under Treated.

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

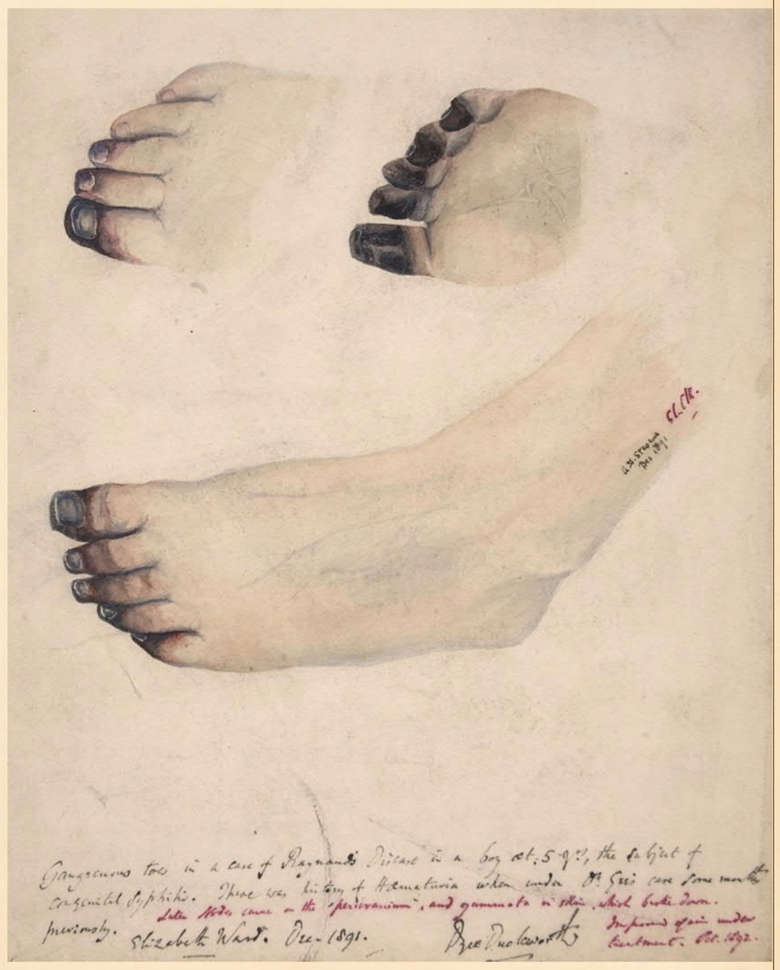



*Mortification, gangrene of the toes. Robert Carswell, London, 1837.*

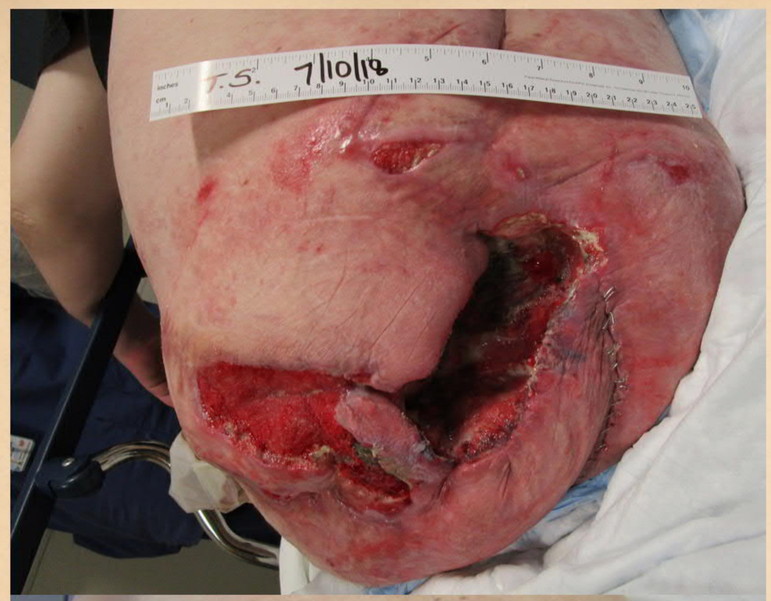
*Dry gangrene after ligature of popliteal aneurism. Thomas Godart, London, 1880.*

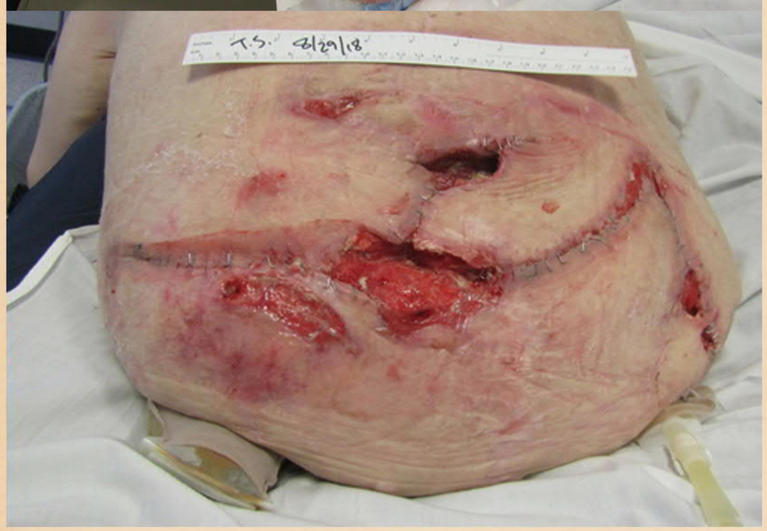


*Gangrene of the hand from idiopathic arteritis. Thomas Godart, London, 1880.*



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




Photos at beginning not available.

**Four months into effective care.**

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

— BUT ALSO —

**Four weeks absent from hospital.**

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

Prompt correction after starting steroids and argatroban.

---

**50 day interval from above image.**

Small incidental wounds all healing.

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

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

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

## UNDERLYING PROBLEM

**34 m :: Paraplegia and pressure ulcers.**

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

Recent onset severe Rheumatoid arthritis.

## STATUS AT ACCEPTANCE

**TLA infarcted, complex abdomino-pelvic wounds.**

## SUCCESS AFTER:

Proper wound care.

Coagulation w/u then Rx.

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

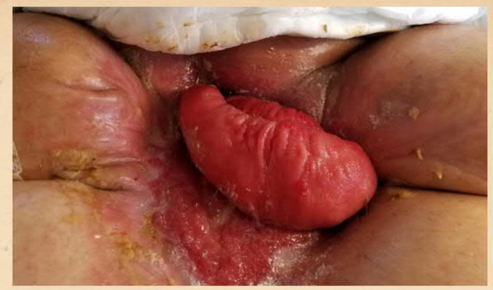
**Continuous argatroban during & after surgery.**

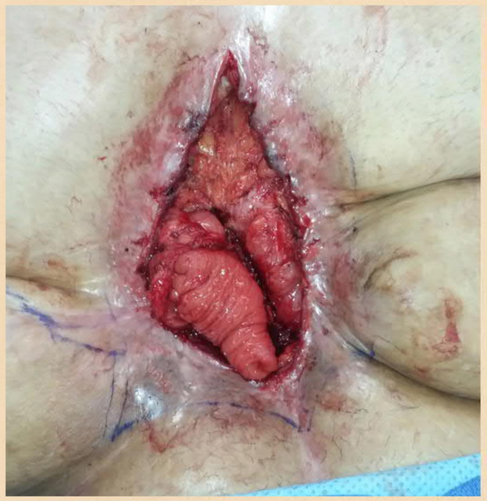
Steroids & multimodal Rheumatoid Rx.

**Proper staged surgery.**

### Positive Lab Studies

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



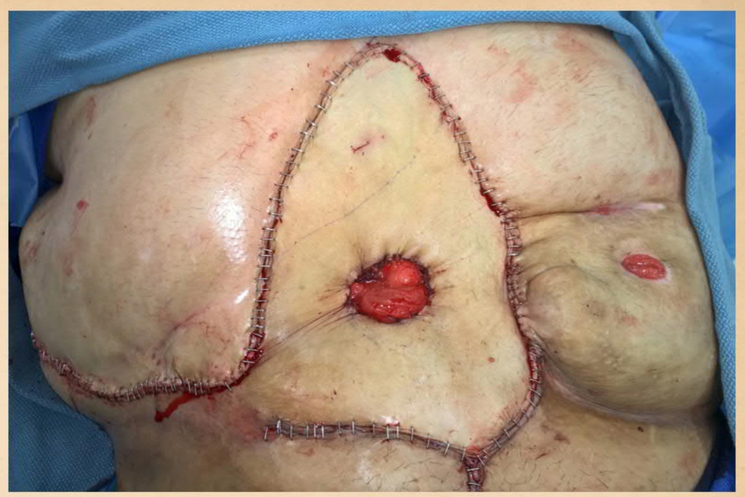


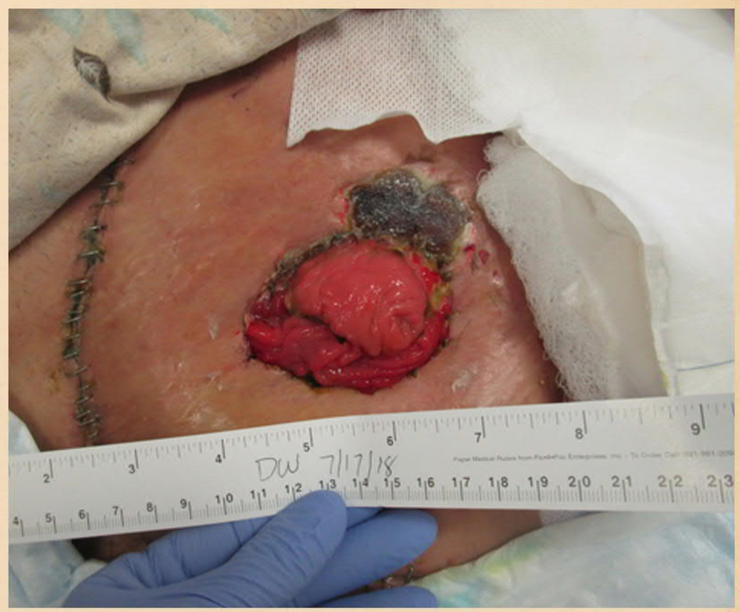
**Left top**, wound & fistula.

**Left bottom**, start of the exposure.

**Right top**, completed surgery with stoma through hypogastric flap.

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






## UNDERLYING PROBLEM

**52 m :: Diverticulitis & complications.**

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

Multiple infarcts & leaks: bowel, anastomoses, wall.

## STATUS AT ACCEPTANCE

**Complex abdominal wound, open bowel & fistula.**

## SUCCESS AFTER:

Proper wound care.

Coagulation w/u then Rx.

**Heparin, then apixaban.**

**Continuous heparin during & after surgery.**

Inflammatory bowel disease ruled out.

**Proper staged surgery.**

### Positive Lab Studies

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

# A NOMENCLATURE OF THROMBO- & MICRO-OCCLUSIVE DISORDERS

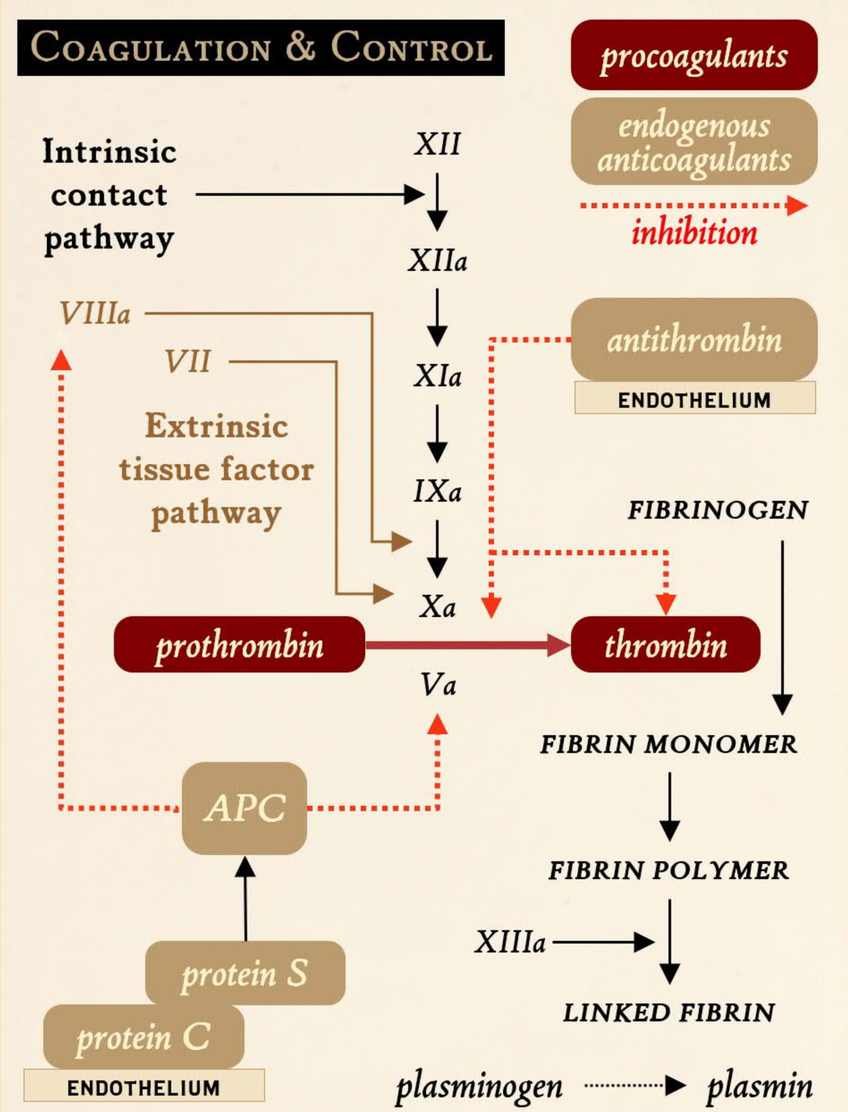
| | | |
|---|---|---|
| Hemodynamic Disorders | vessels, blood, & coagulation normal<br>**Fluid Dynamics Abnormal** | Hemodynamics & macro-vasculopathies<br>*Examples :* a-v malformations, atrial fibrillation<br>vascular compression, low flow states |
| Endo-Vasculopathies | blood & coagulation normal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

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

These categories can each be subcategorized.

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

# COAGULATION PHYSIOLOGY & PATHOLOGY




## 1 - Normal coagulation

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

## 2 - Hypercoagulopathy

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

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

## 3 - Pathophysiology of errant clotting

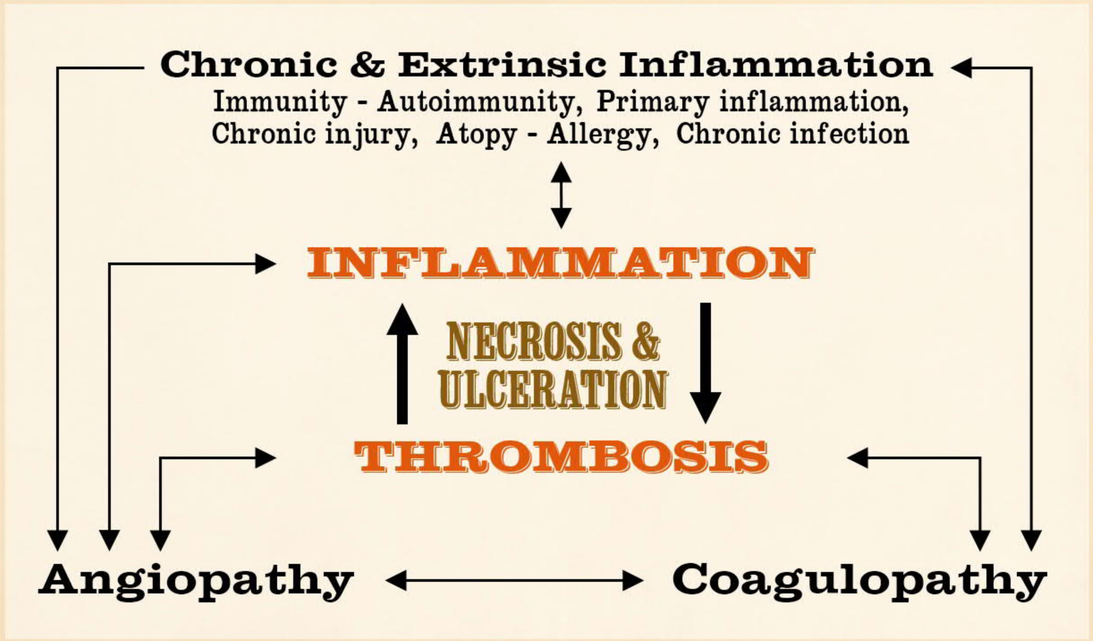
Thrombosis occurs in intact vessels, interrupting blood flow.
Large vessels and structures are at risk for major infarct or death.
Small vessel non-lethal events cause vascular stasis and micro-infarction (becoming ulcers).
Inflammation is triggered. Stasis & inflammation are in turn normal triggers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

## 4 - Biochemistry

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

## 5 - Dynamical disorder

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



# A NOMENCLATURE OF THE HYPERCOAGULABLE DISORDERS

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

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

# CLINICAL PATHOLOGY OF THE HYPERCOAGULABLE DISORDERS

## Macrothrombosis

Large vessel
Acute
Overt
Life and limb risk

---

"Old hat"
Often easily recognized
Defined clinical syndromes

---

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

coronary artery thrombosis
intracardiac thrombosis
graft and valve thrombosis
cerebrovascular thrombosis

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

---

The underlying hypercoagulopathy might nonetheless be overlooked.

## Microthrombosis

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

---

Under appreciated
Often non-obvious
Perplexing refractory problems

---

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

---

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

miscarriage
complications of contraceptives

non-immune glomerulonephritis
primary pulmonary thrombosis
warfarin necrosis

## Related Disorders

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

---

## Disease Associations

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

## Others of Interest

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

---

## Hypercoag Syndrome

***Tetrad – Pentad***

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

## Core Pathophysiology

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

***Hypercoagulable blood clots spontaneously within normal vessels.***

---

## Cf. Hypocoagulability

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

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

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

# NECROSIS & ULCERATION – TWO GENERAL PATHOLOGIES & PATTERNS

## THROMBO-INFARCTIVE

*The pattern of ischemia and stromal deprivation.*

**Macro-occlusive**

**Micro-occlusive**

**Micro-angiopathies**

**Hemopathologies**

**Hypercoagulable / Coagulopathic**

## INFLAMMATORY-LYTIC

*The pattern of inflammation and stromal predation.*

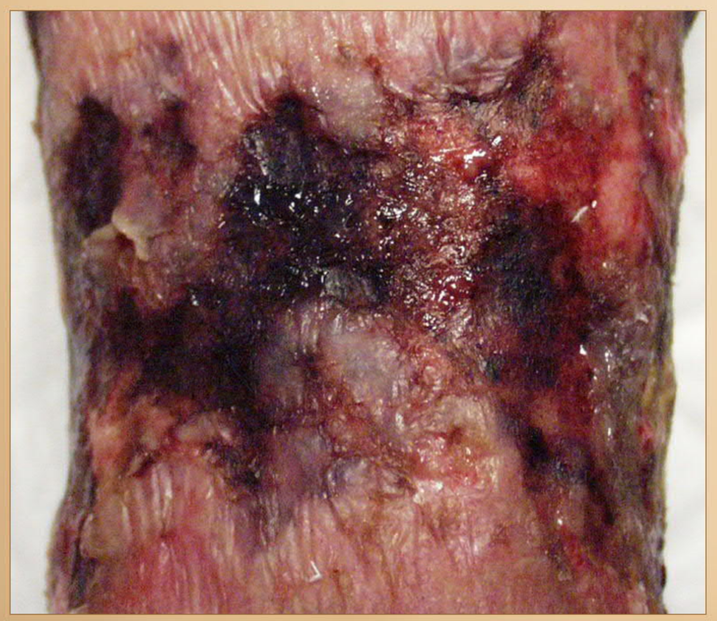
**Inflammatory**

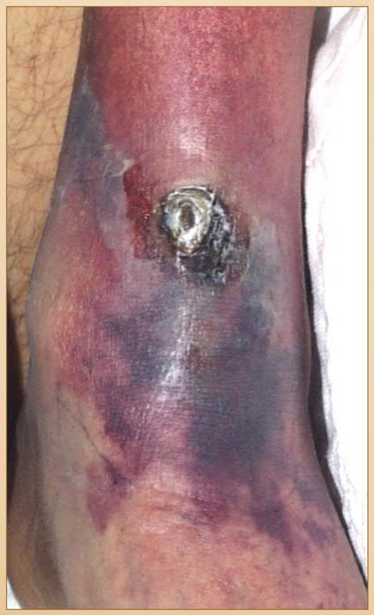
**Autoimmune**

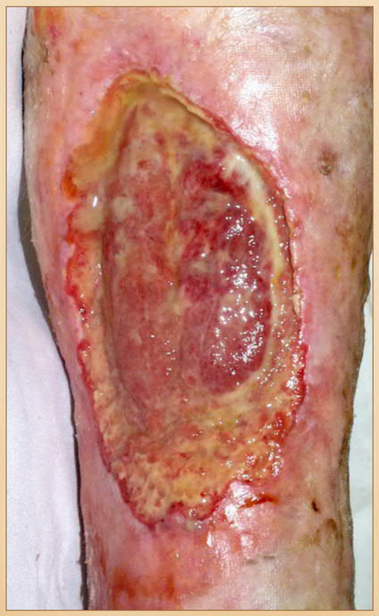
**Atopic, Suppurative**

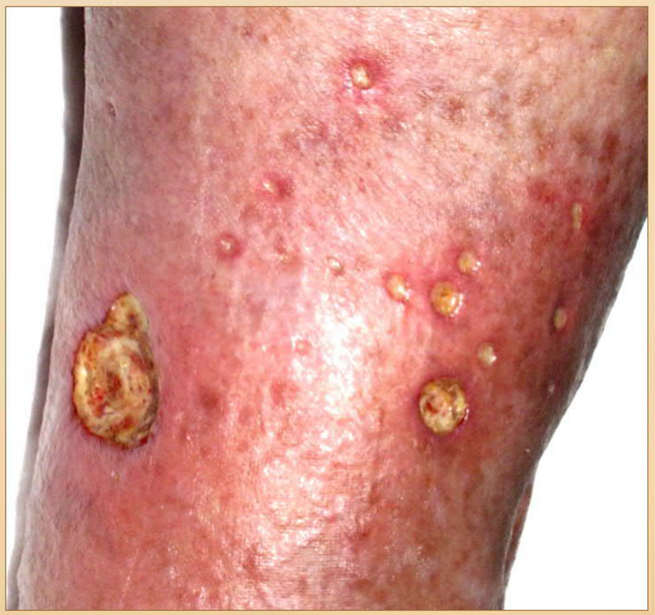
**Connective Tissue Disorders**

**Lymphoreticular / Reticuloendothelial**









# CLINICAL PATHOLOGY OF HYPERCOAGULABLE WOUNDS & ULCERS

## Onset of Illness

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

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

Common on lower extremities.
Can occur anywhere.

## Link to Inflammation

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

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

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

## Findings

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

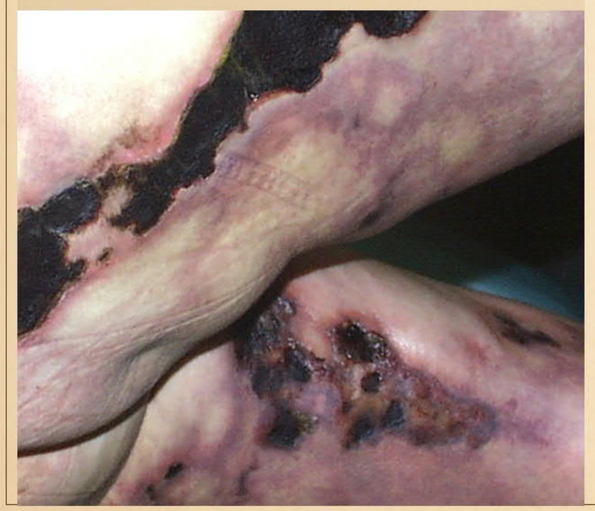
Periwound stasis, low TcpO2, pain.
Mixed wound module, non-healing.
No signs of other dx.
Good pulses.

Confirmatory blood tests & histology.

### Acute necrosis.

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

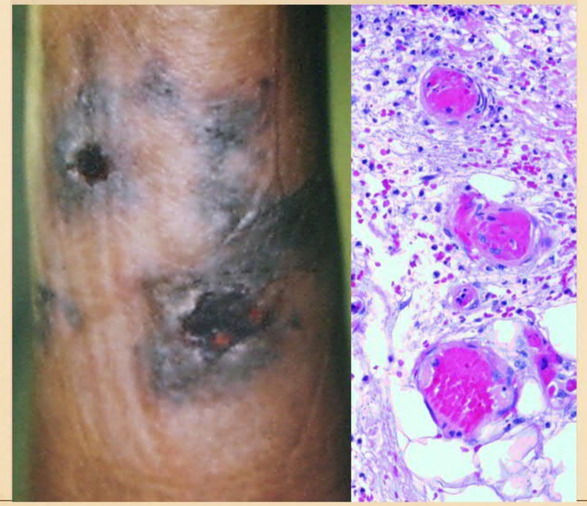
***35 yo woman, acute lupus.***
*Extensive skin infarcts (hips & thighs shown). Antiphospholipid antibodies. Low skin TcpO2s.*



### Stasis and infarcts.

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

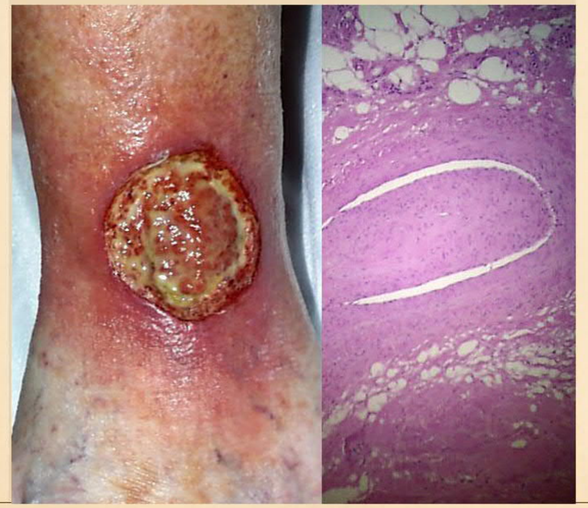
***43 yo man, spontaneous leg ulcers.***
*Very low proteins C and S (leg & ankle shown). Small vessel thrombosis and organization, with adjacent stasis, congestion, and hemorrhage.*



### Chronic active ulceration.

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

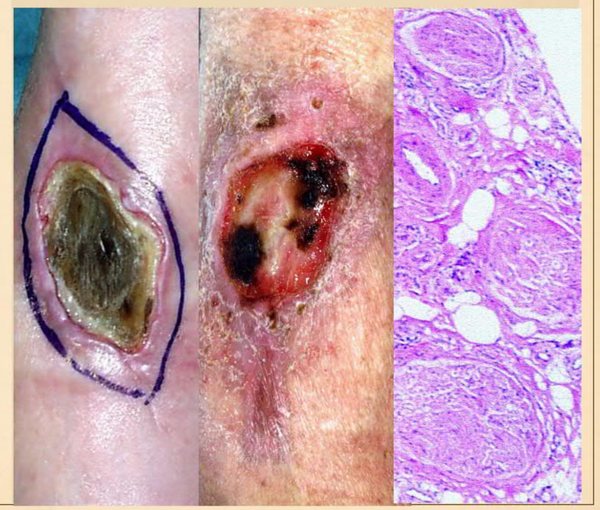
***61 yo woman, protein S deficiency.***
*Long history DVT, PE, and leg ulcers. Perpetual stasis, inflammation, active infarction and ulceration. Old recanalizing thrombus shown.*



### Trauma pathergy, morbidity.

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

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



# CLINICAL PATHOLOGY OF HYPERCOAGULABLE WOUNDS & ULCERS

## Dynamical Behavior

refractory impaired wound behavior
characteristic of severe ischemia

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

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

## Complications

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

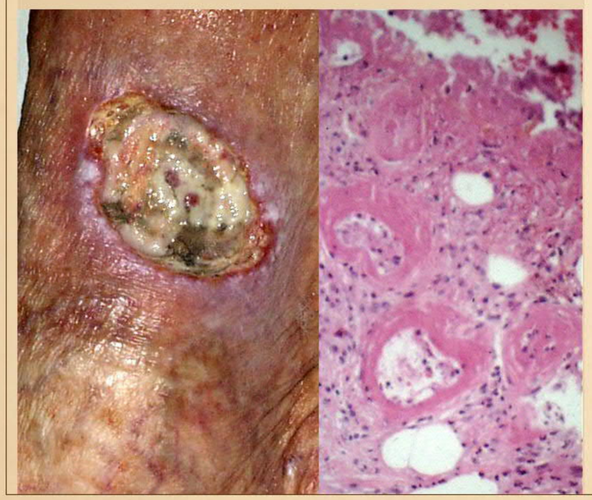
## Treatments & Outcomes

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

### Surgical complications.

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

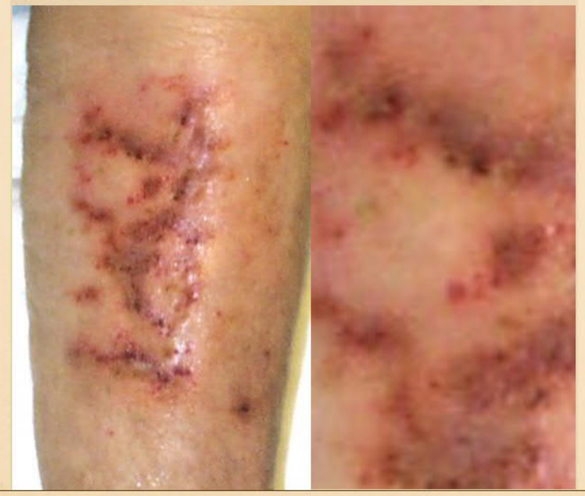
***69 yo woman. Wound dehiscence.***
*Complication of active ulceration after biopsy for minor skin lesion. Protein S deficient, and cryoglobulins. Histology shows thrombi, vessel and tissue necrosis.*



### Failed therapy.

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

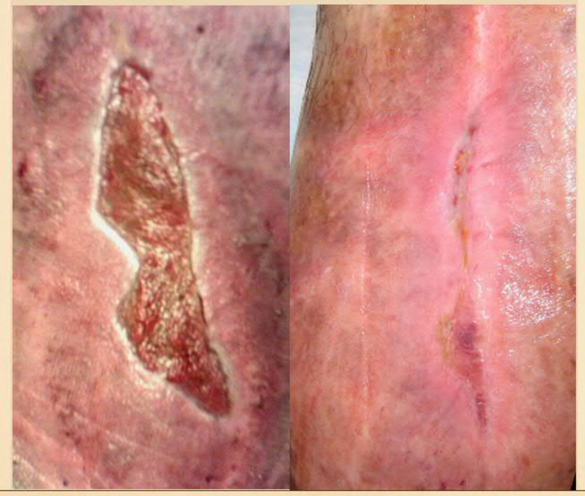
***72 yo woman, high anticardiolipins, ANA.***
*Ulceration and impaired healing of primary leg wound; then same for skin graft donor site, stasis & infarcts shown.*



### Unexpected profiles.

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

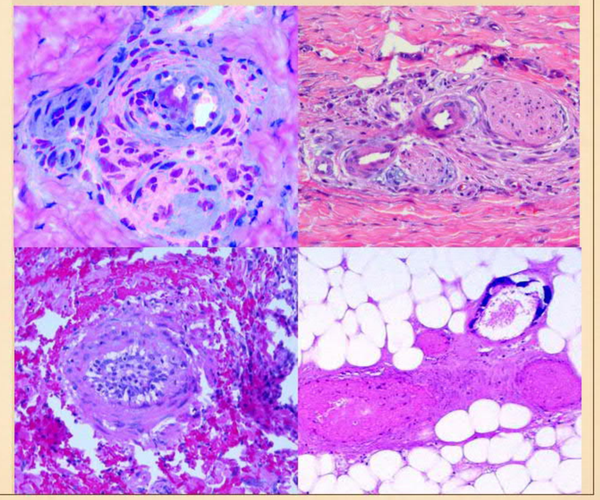
***39 yo man. Refractory leg ulcers.***
*Chronic since femur fracture & DVT at age 14. F.V Leiden (young men with venous ulcers have this mutant gene). Healed with 2 months of warfarin.*



### Histology.

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

***4 patients with various diagnoses.***



# DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

## 1-A · Personal History

**Any recurrent, unexpected, or inexplicable thromboembolism**

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

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

**Related diseases and events**

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

**Hypercoagulable ulcers are NOT diagnoses of exclusion.**

*These diagnoses can be made on specific criteria.*

## 1-B · Family History

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

miscarriages
thrombosis & embolism
autoimmune disease

## 1-C · Wound & Tissue History

**Wounds and ulcers**

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

**Other events**

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

## 2-A · Physical Exam - Wound

**Distinctive or consistent findings**

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

**Discrimination from other diagnoses**

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

# DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

## 2-B · Physical Exam - General

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

## 2-C · Exam & F/u - Response to Rx

### Failures of general care

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

### Complications of specific care

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

### Aberrant Response to Care

warfarin necrosis
warfarin resistance
difficulty regulating PT-INR

*"things that just don't add up"*

**Hypercoagulable ulcers are NOT diagnoses of exclusion.**

*These diagnoses can be made on specific criteria.*

## 3-A · Lab - Clinical

### General studies

CBC, platelet, CMP, U/A

### Thrombotic species

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

### Immune procoagulants

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

### Autoimmune

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

### Other micro-occlusive

SPEP / SIFE
PF4, Hgb, cryoglobulins, cryofibrinogen
*new and future tests*

## 3-B · Lab - Special

### Vascular

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

### Histology

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

## 3-C · Differential Dx & R/O

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

# DIAGNOSIS & APPROACH TO THE HYPERCOAGULABLE DISORDERS

## Interpretation of Common Hypercoagulable Tests

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

**Hypercoagulable disorders & ulcers are NOT diagnoses of exclusion.**

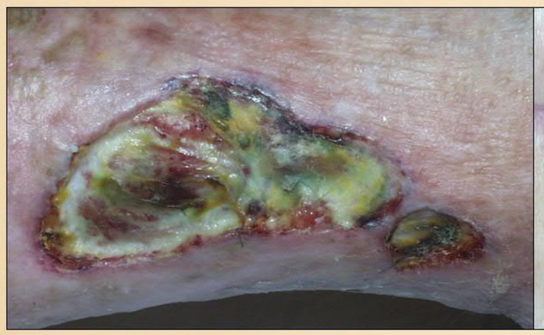
*They can be made on specific criteria.*

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

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

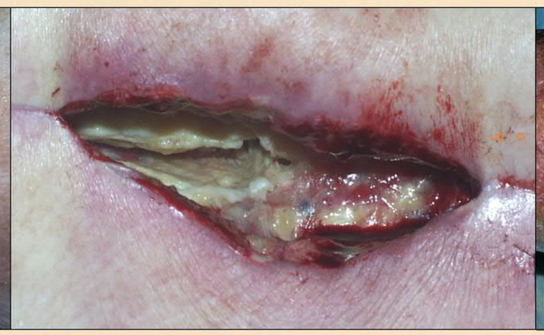
If history and physical are equivocal,
positive blood tests are confirmatory.
*(Remember, tests were ordered for suspicion.)*

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



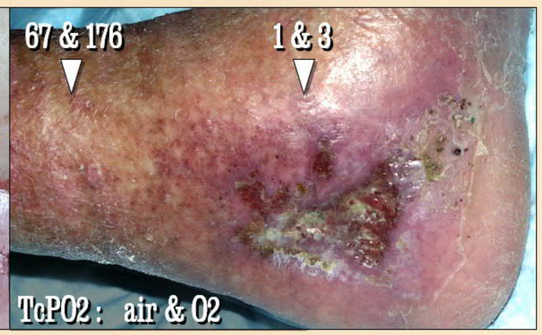
**78F Sjögren's**

| | | |
|---|---|---|
| fibrinogen | 565 | ++ |
| protein C | 60 | – |



**67F Rheumatoid Arthritis**

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




**57M Cirrhosis**

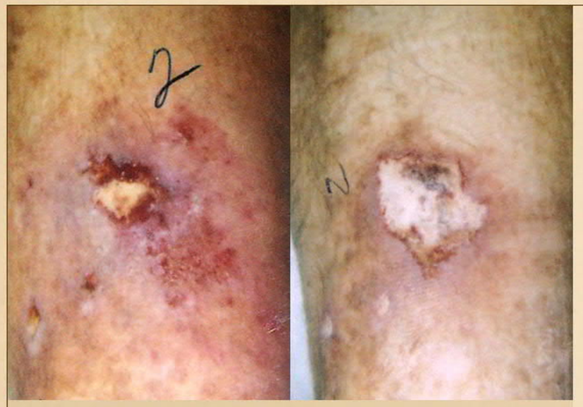
| | | |
|---|---|---|
| bili | 2.1 | + |
| alk phos | 160 | + |
| RF | 44 | + |
| ANA | 1:80 | + |
| AT-III | 47 | – |
| protein C | 35 | – |
| protein S | 55 | – |

## The Hypercoagulable Syndrome

**Tetrad – Pentad**

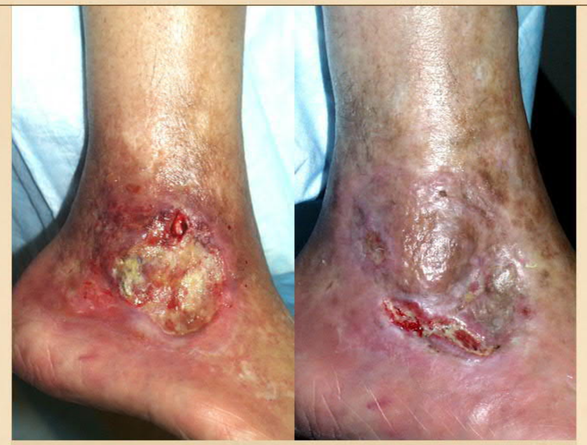
**Thrombotic or embolic event**
**Autoimmune cvd-ctd**
**Wound pathergy**
**Miscarriage**
**Family history of same**

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



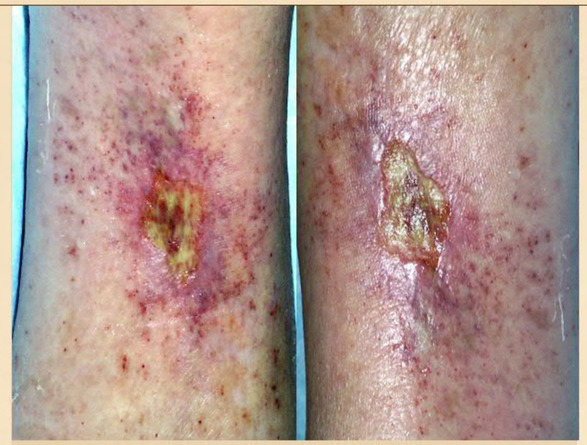
## 54M No prior diagnosis

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



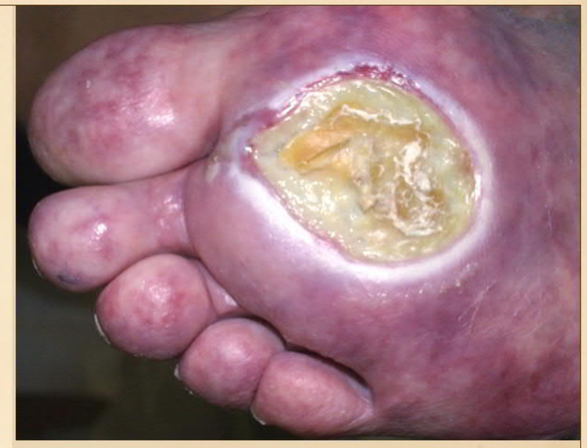
## 66F Scleroderma / MCTD

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



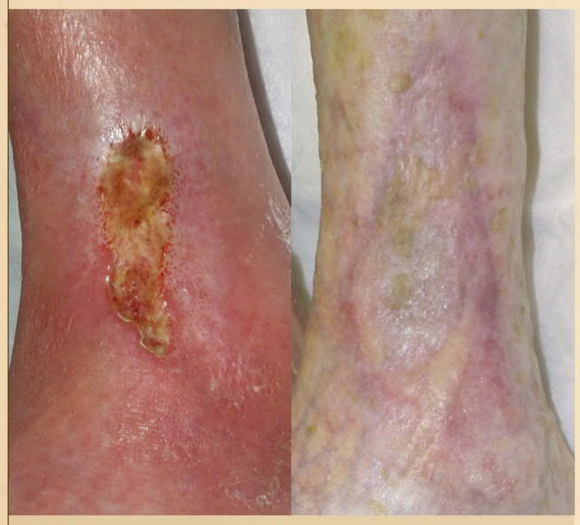
## 81F Leg ulcer

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



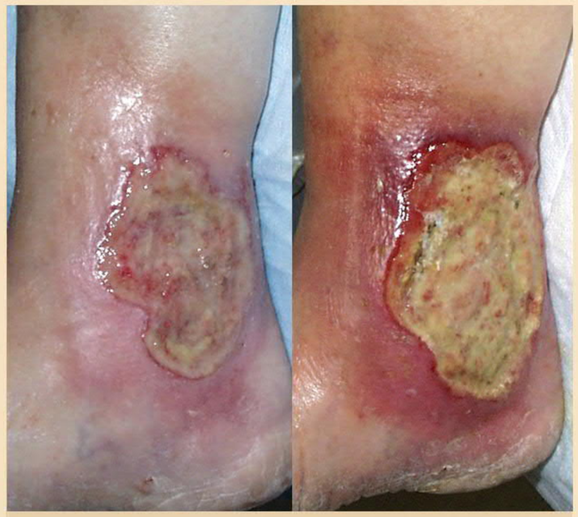
## 76F Scleroderma

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



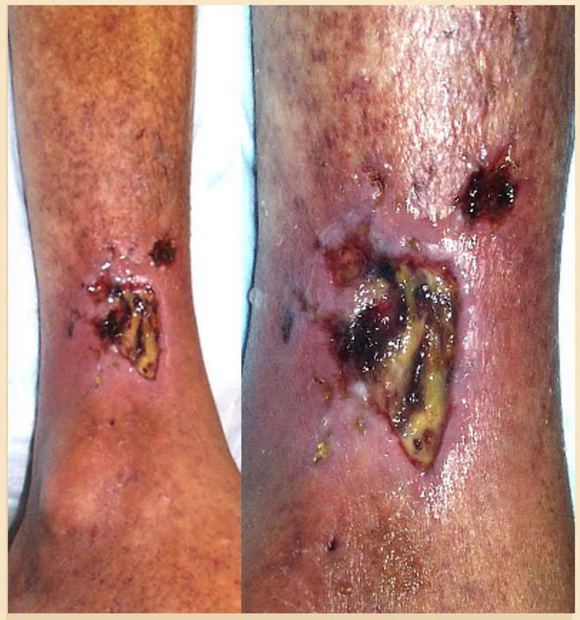
## 69F Rheumatoid

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



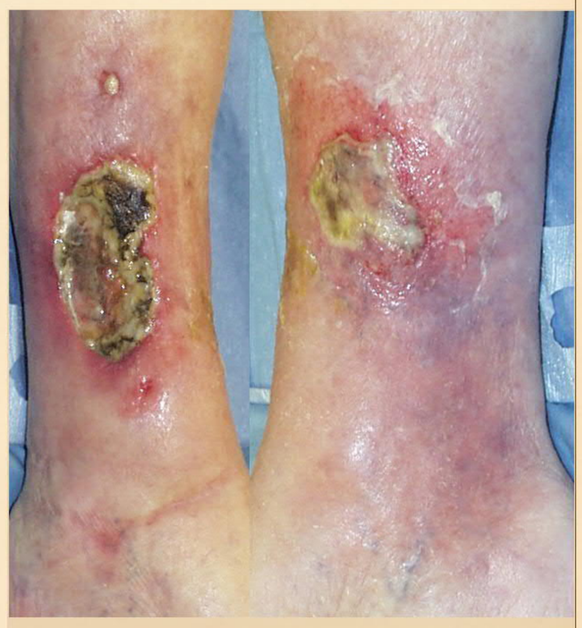
## 72F Polycythemia Vera

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



## 75M Anemia / Cythemia

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



## 80F Leg ulcers, brain infarct

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

# TREATMENT & MANAGEMENT OF THE HYPERCOAGULABLE DISORDERS

## 4-A • Management - General

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

**Associated risks and diseases**
treat each accordingly
workup & treat immunopathies

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

of uncertain relevance:
anti-platelet drugs
rheologicals

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

## 4-B • Management – Wounds & Tissues

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

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

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

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

## 4-C • Management – Long Term

**General**
manage underlying diagnoses
control associated risks & triggers

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

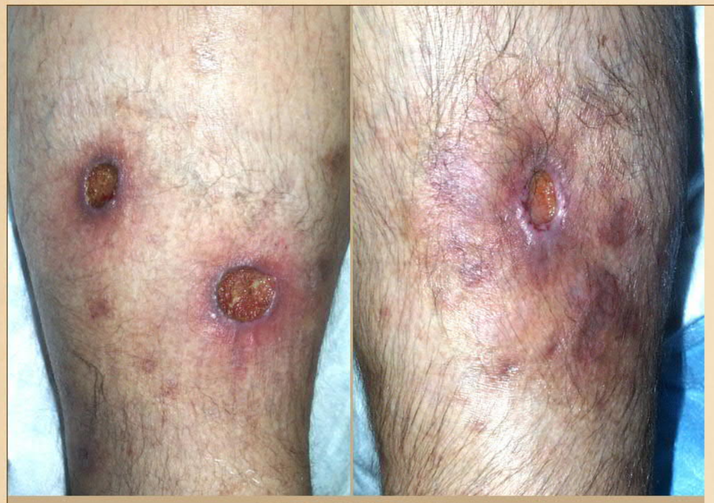
**Anticoagulation**
until healed, plus 3-6 months
limited use for antiplatelet drugs
long term or lifetime anticoagulation,
*(depending on diagnosis and risks)*

**PROPHYLAXIS FOR PROCEDURES**

### Principles of Anticoagulation
### Restoration of Normal Profile

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

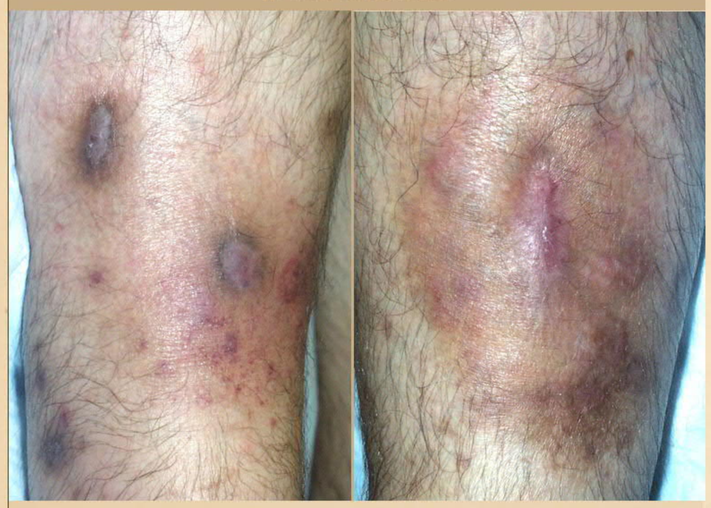
After adequate anticoagulation, necrosis stops, tissues start to revascularize, and wound healing resumes.



BEFORE WARFARIN

RIGHT LEFT

AFTER WARFARIN



**29 M**

Multiple leg ulcers, many years.
*Suspicious history.*

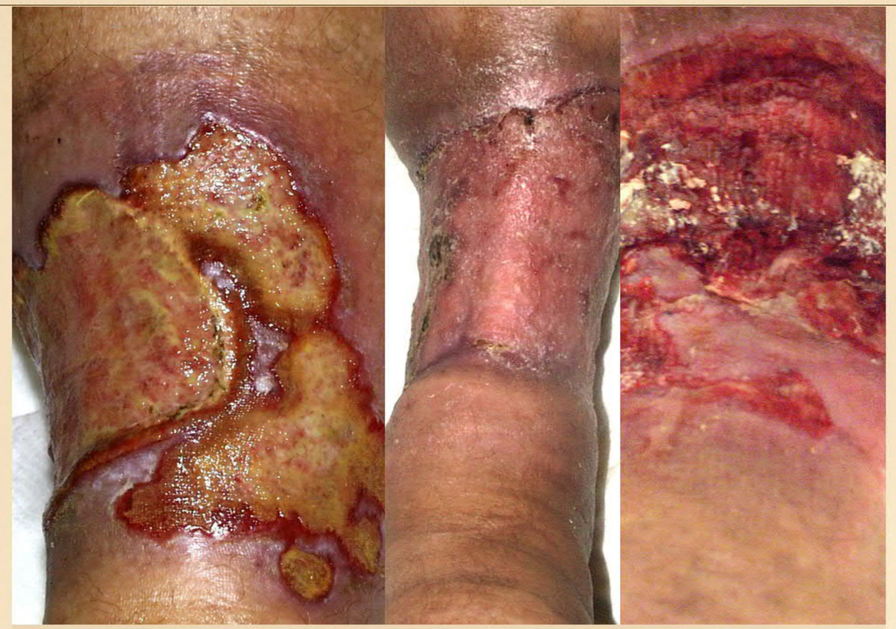
Otherwise healthy.
*No other illness or explanation.*

Family history multiple miscarriages.
*Family history.*

Lab: **high anticardiolipins**.
*Confirmatory blood tests.*

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

**Dx: Antiphospholipid antibodies**



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

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

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

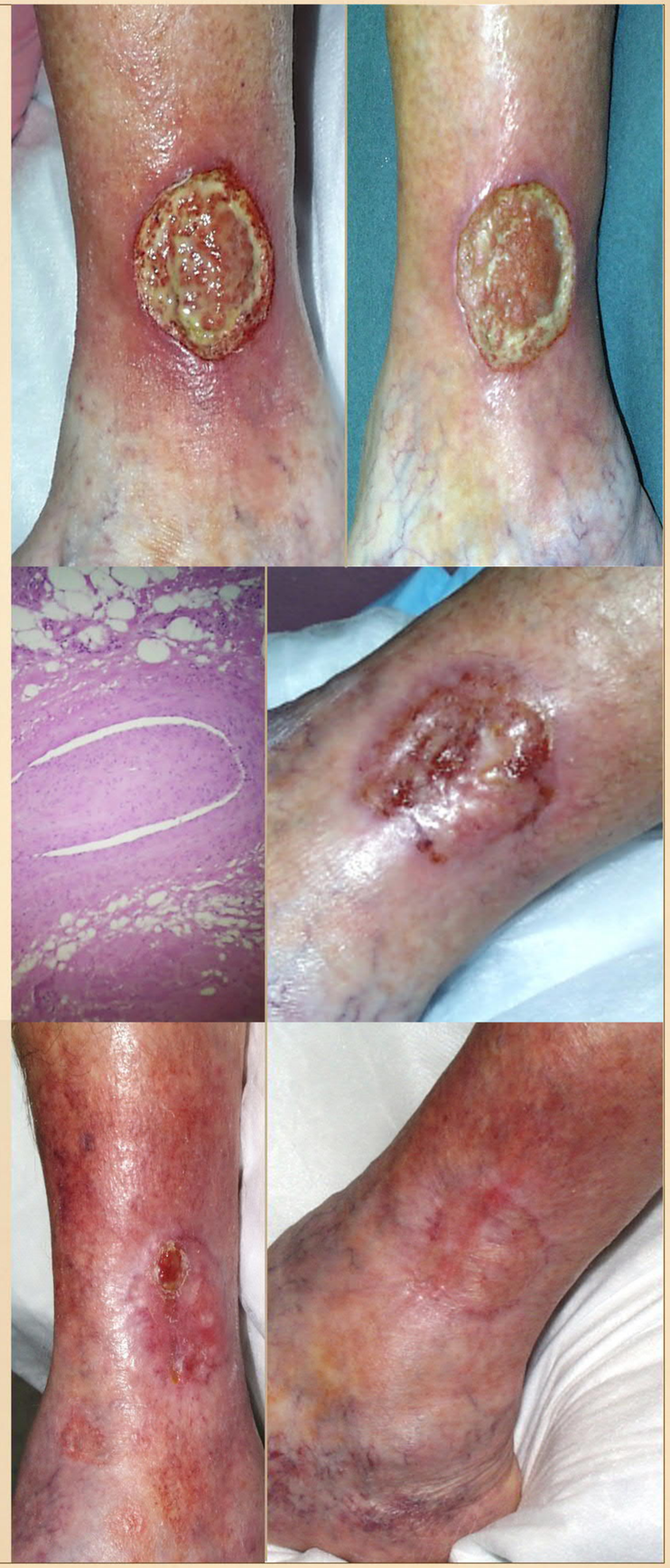
Healed after high-INR warfarin (*& regenerative biomatrix*).
Recurrence after lapsed warfarin.
*Characteristic response to anticoagulation.*

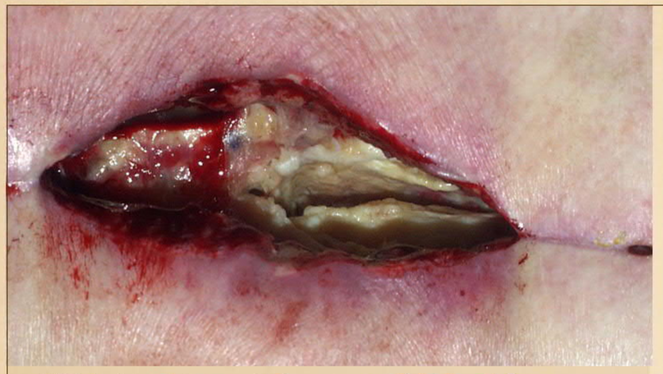
**61 F** **Dx: Protein S deficiency**

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

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

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





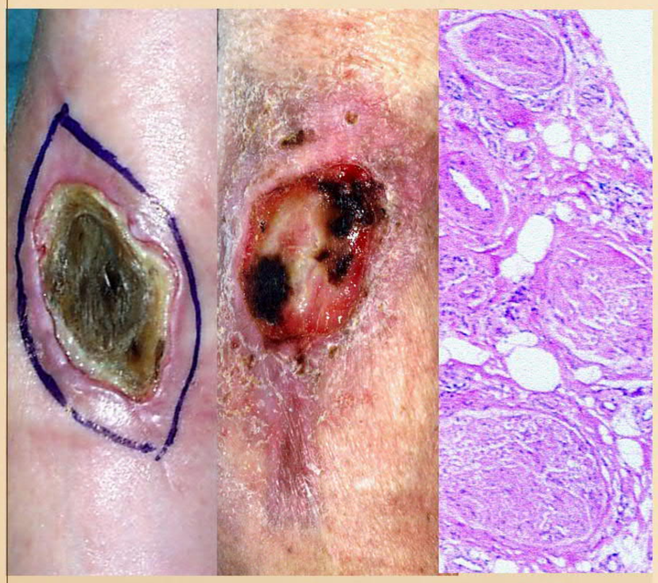
**67 F** **Dx: Factor V Leiden**

Back wound necrosis after spine surgery.
Family hx strong for DVT & leg ulcers.
*Suspicious history.*

Thrombo-infarctive, vascular stasis.
*Confirmatory exam.*

Lab: **Factor V Leiden, fibrinogen high.**
plasminogen & protein C high.

Healed: warfarin, then surgery.

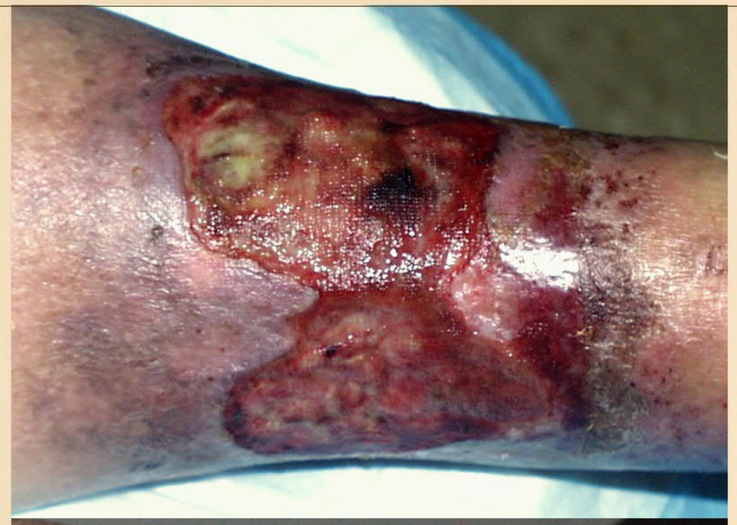


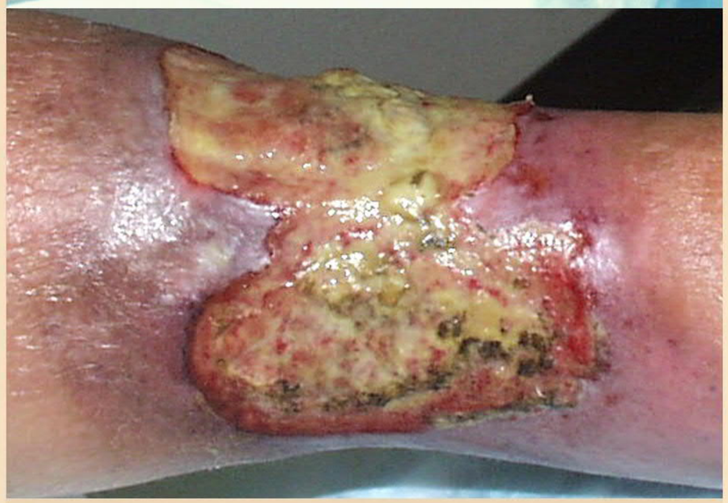
**53 F** **Dx: C & S deficiency**

Wound infarct after dogbite injury, u.e.
Multiple failed surgery. Rheumatoid.
*Suspicious history.*

Lab: **protein C low, protein S low.**
histology - thrombus, organization.
*Confirmatory tests.*

Healed: warfarin, biomatrix.
Late re-ulceration after warfarin stop.
*Proper wound behavior only after warfarin.*





**46 F**

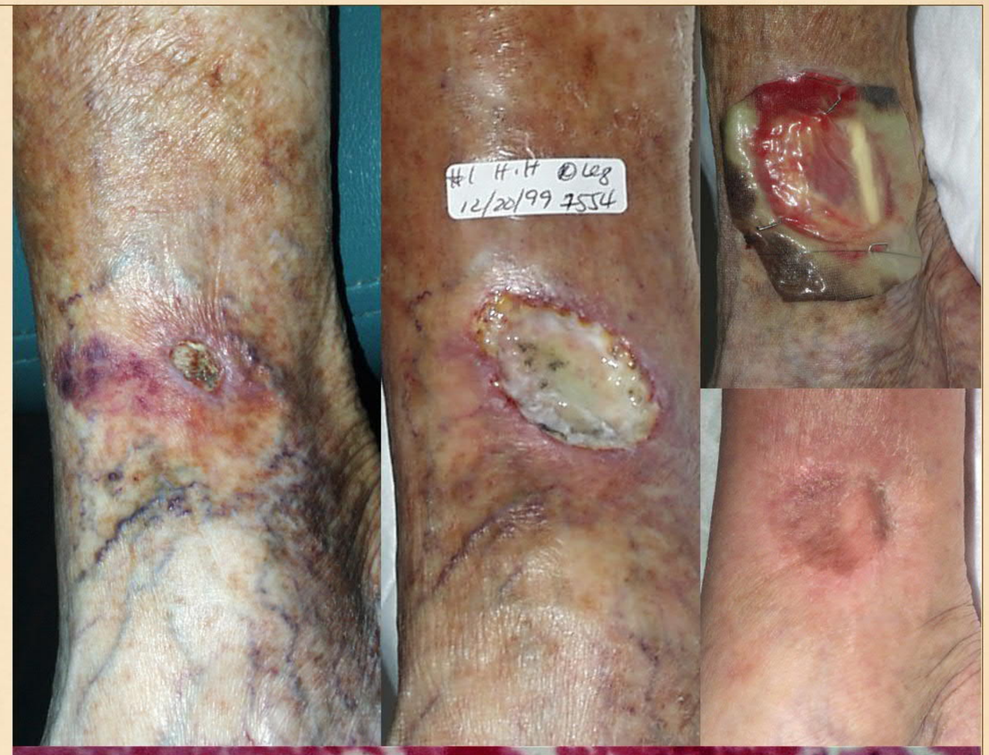
Refractory active ulcers.
Multiple miscarriages.
*Suspicious history.*

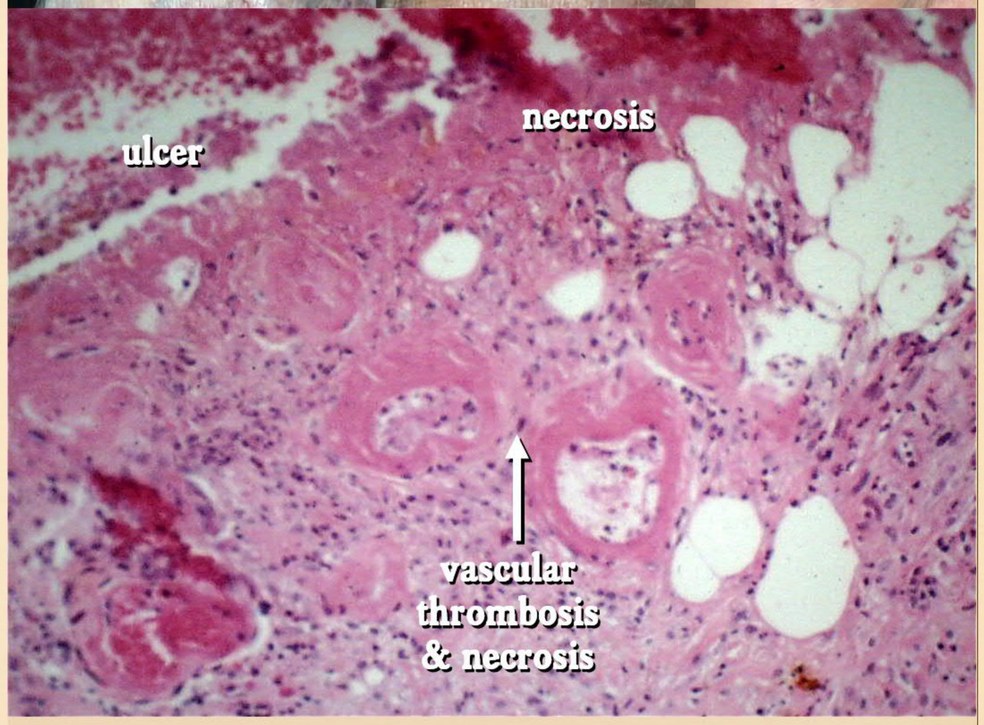
Mixed but mainly thrombo-infarctive pattern.
Good pulses in feet.
*Confirmatory exam.*

Lab: **prothrombin 20210G mutation.**
**homocysteine very high.**
**p-anca & anti-mpo high.**
*Confirmatory blood tests.*

Healed: warfarin, etc.
*Healing on anticoagulation.*

**Dx: Primary hypercoagulopathy**
**Secondary immunopathy**



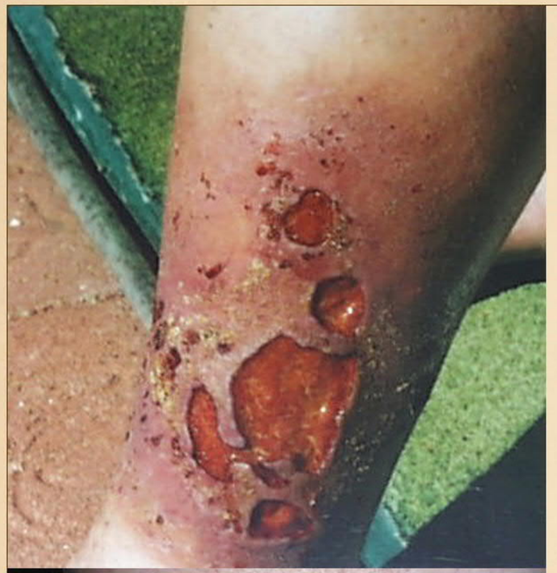

**69 F** **Dx: mixed coag**

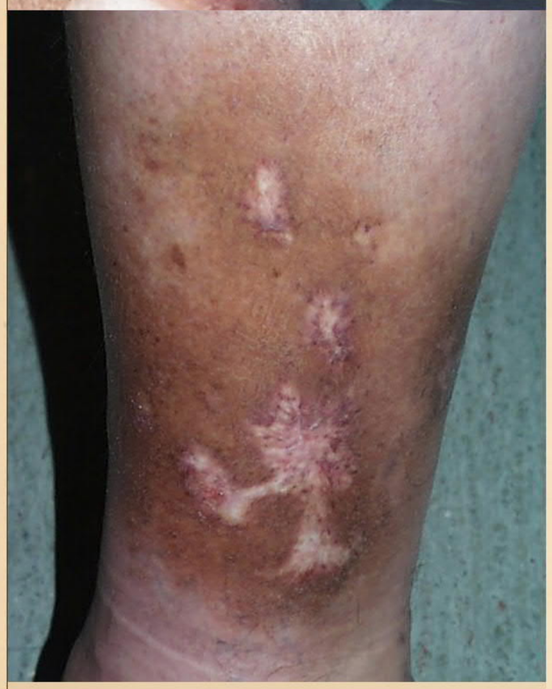
Spontaneous skin ulcer.
Venous perforator thrombosis.
Wound pathergy after biopsy.
*Suspicious history and exam.*
*No prior illness or explanation.*

Lab: **protein C low.**
**cryoglobulins present.**
*Confirmatory tests.*

Healed: warfarin, biomatrix.

*Proper behavior only after warfarin.*



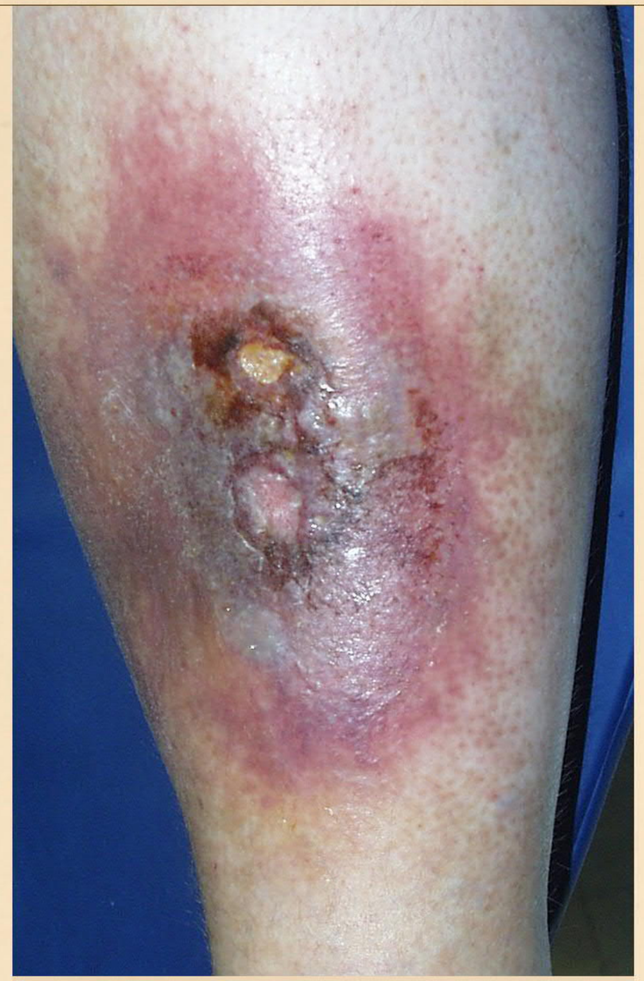


**42 M**

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

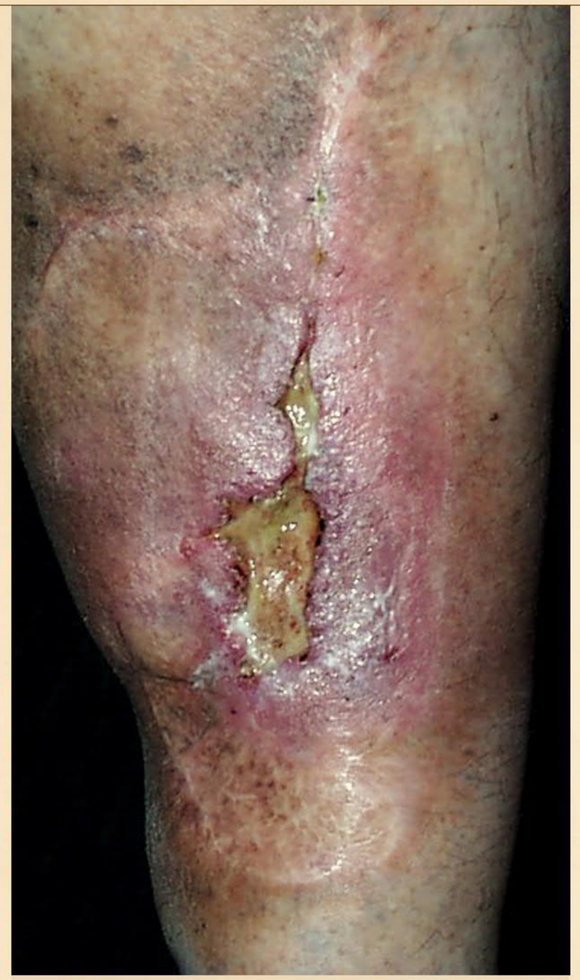
Lab:
protein C & AT-3 low.
anticardiolipins high.
homocysteine high.
f.V Leiden heterozygous.
*Confirmatory blood tests.*

**Dx: Multi-factorial hypercoagulopathy**



**38 M** **mixed hypercoag**

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



**33 M** **venous disease**

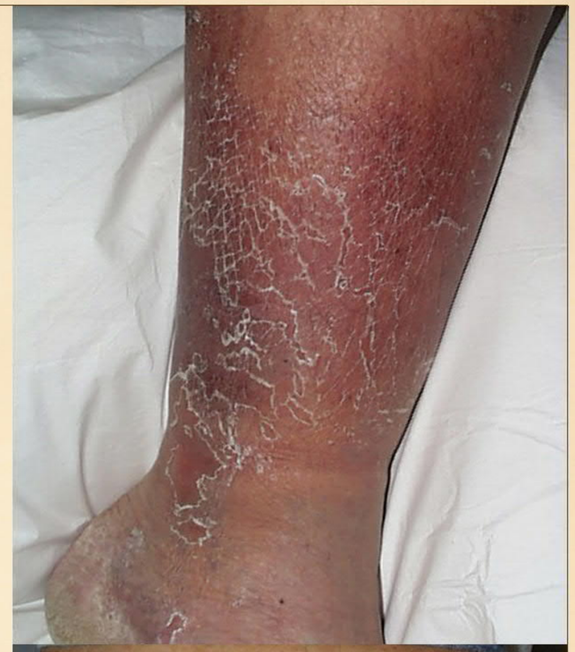
Refractory leg ulcer, many years.
DVT after femur fx, age 9.
*Suspicious history.*
Lab: f.V Leiden heterozygous.
*Confirmatory blood tests.*

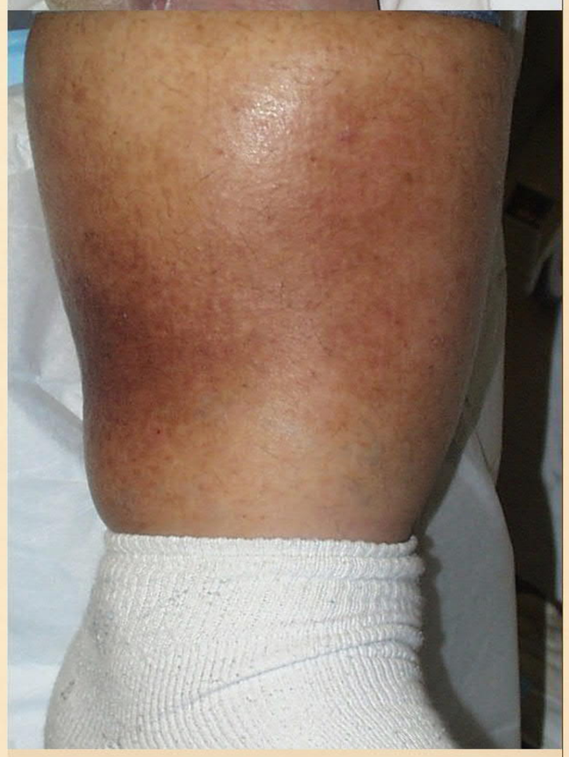
## Young men with chronic Venous Disease.

***Venous hypertension, panniculitis & dermatitis, ulceration.***

**Classical clinical syndromes yield to new understanding.**

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

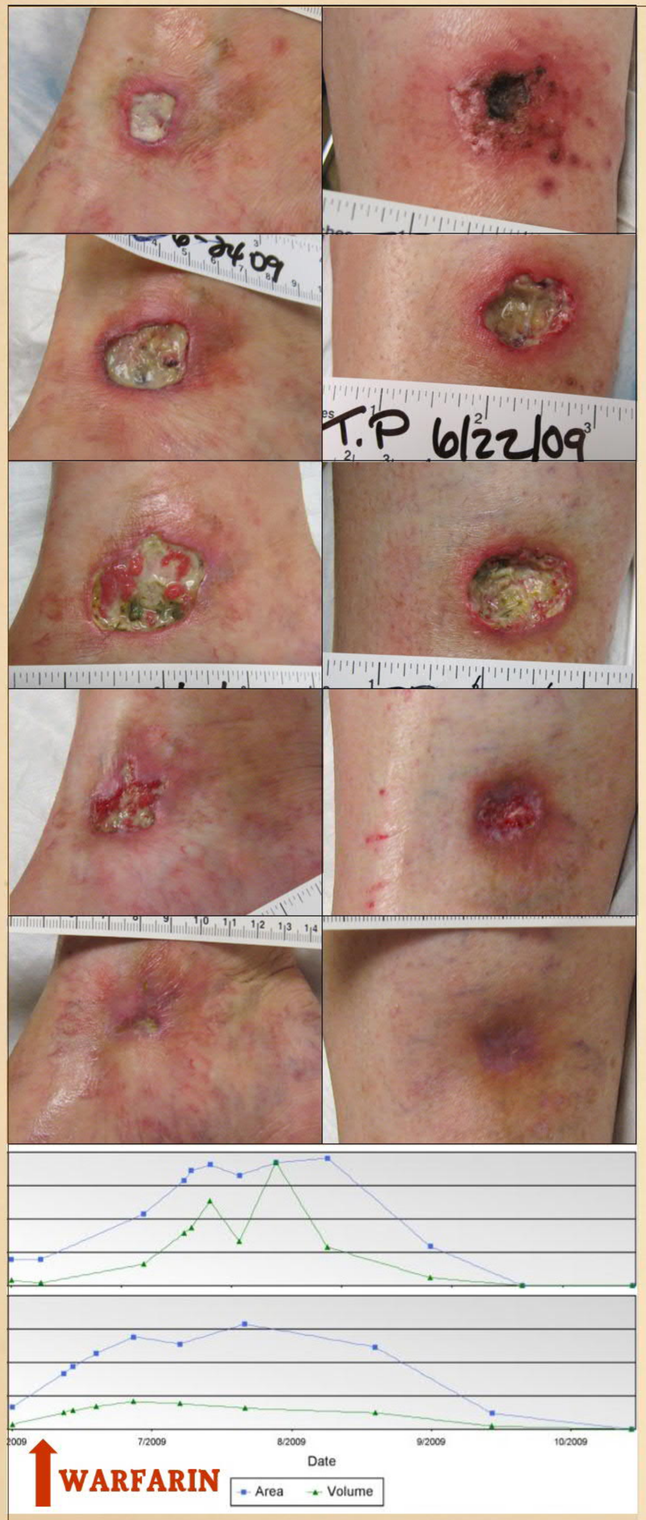




**42 M** **venous disease**

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

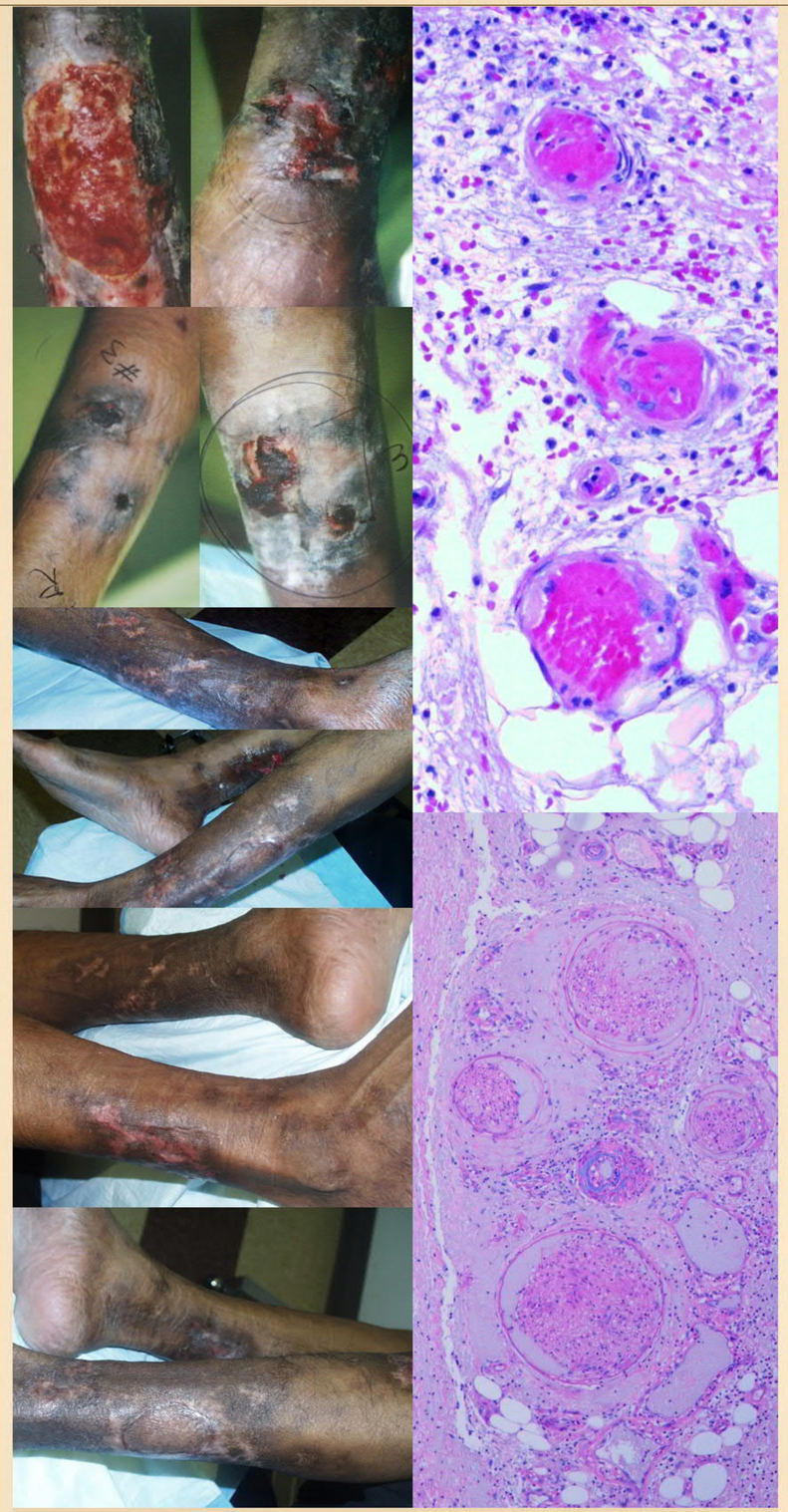
*(Top, active before rx; bottom, 1 year later.)*




**57 F** **Factor V Leiden Hetero**

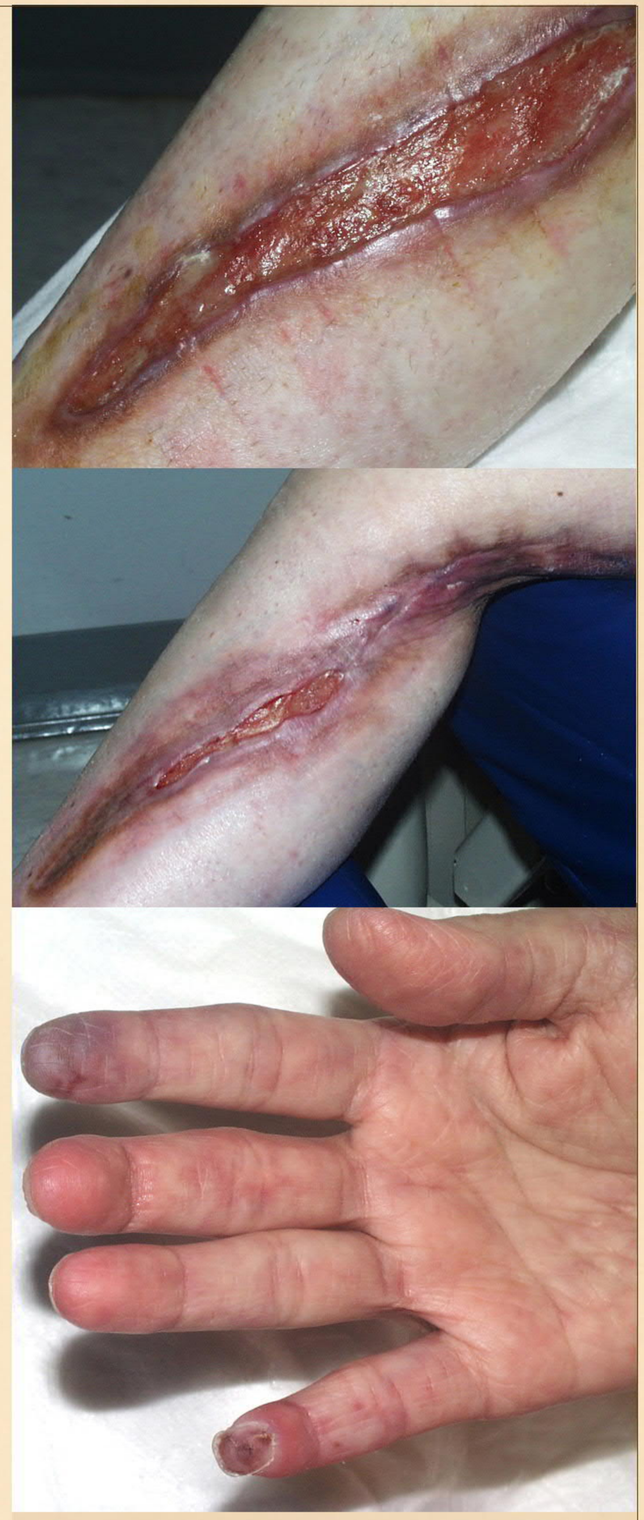
Acute leg & ankle skin infarcts & ulcers.

**Healed by warfarin only** (& basic topicals).



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

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

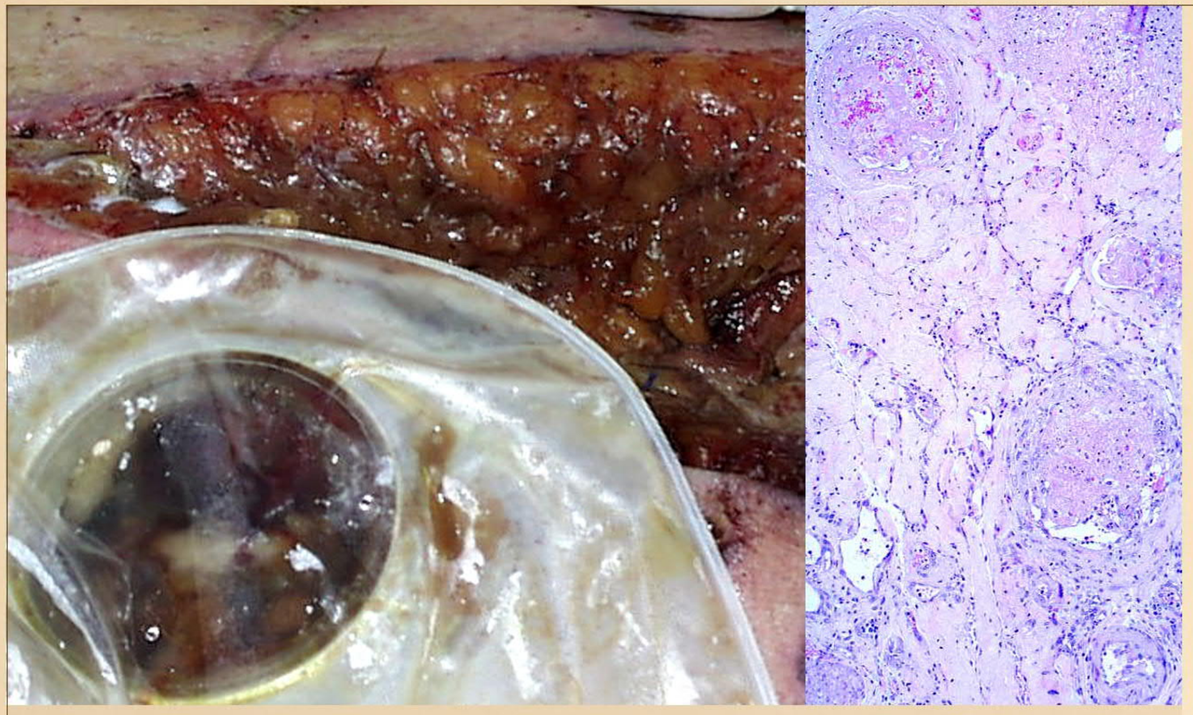


**38 F** **Lupus, APL syndrome**

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

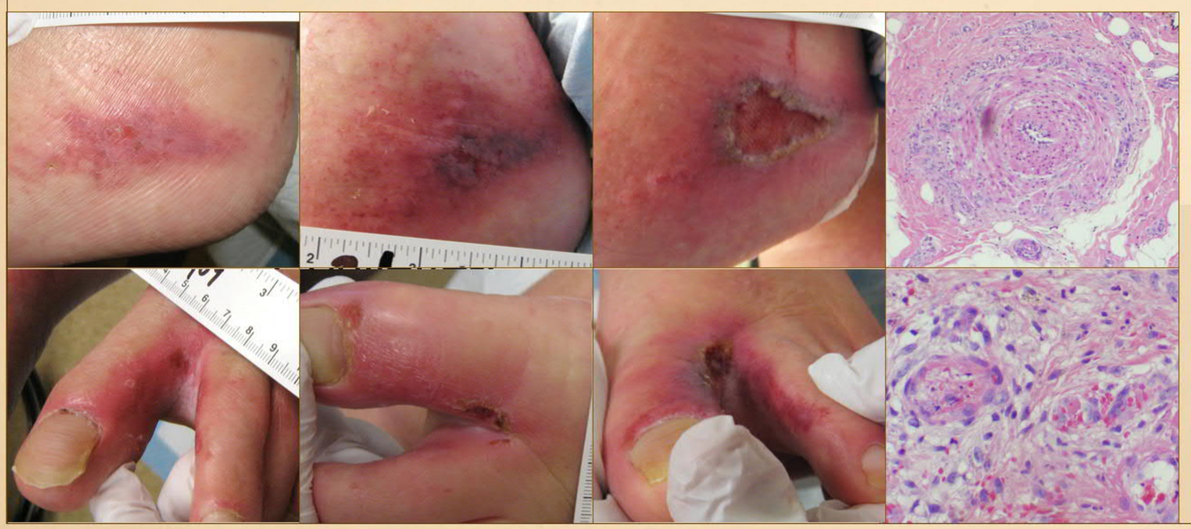
**Note the potency of anticoagulants alone to restore normal wound healing, allowing eligible wounds to heal by natural contraction.**

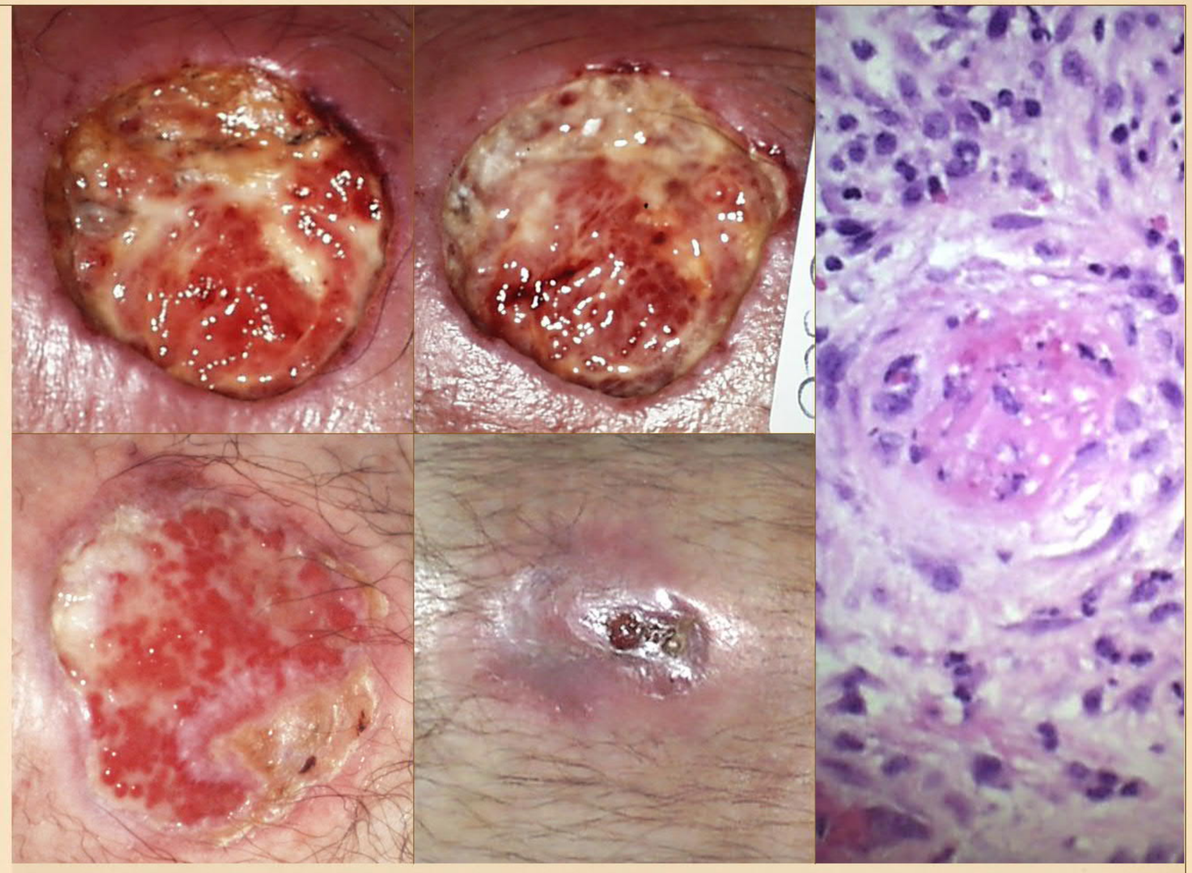
# Hypercoagulable Disorders – Implications for Wound Pathergy, Acute Wounds, Chronic Ulcers, Trauma, and Surgery.



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

Diverticular colo-vesical fistula.
Wound pathergy, then multiple infarcts and complications after surgery.
Bowel necrosis, abdominal wall necrosis.
Hx DVT - PE.
Hx finger necrosis after minor trauma.
*Suspicious history.*
Lab: APC resistance high.
*Confirmatory tests.*
Died before anticoagulation and diagnosis-specific Rx.





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

Wound pathergy, then multiple failed surgery after trivial hand trauma.
Multiple subsequent wounds from failed grafts and flaps.
Second set of wounds after elective hip replacement (for lupus arthritis).
*Suspicious history.*
Lab: anticardiolipins high.
*Confirmatory tests.*
Healed by warfarin only (& basic topicals).
*Proper wound behavior only after warfarin.*
Later: mva, abdominal trauma, abdominal wall infarct with wounds & colon fistula.
Later: home fall, minor non-skeletal back injury, tardive 2° cord infarct, paraplegia.

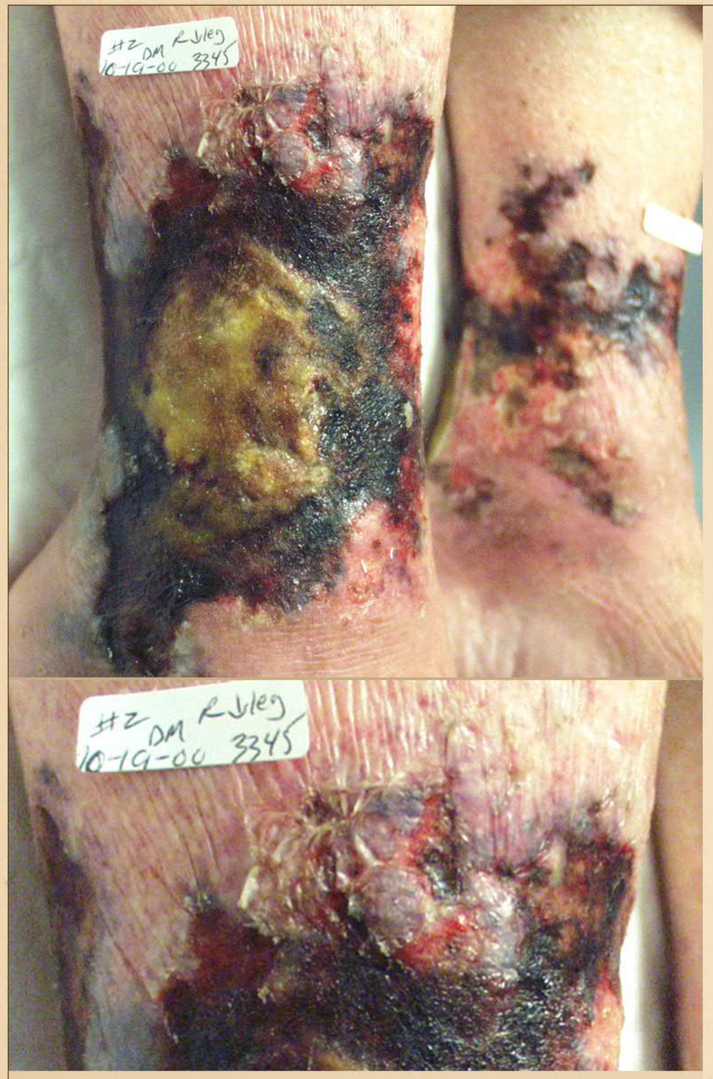
**39 M** **Dx: Factor V Leiden**

**Tardive paraplegia from non-skeletal non-cord back injury**

Minor fall without spine injury or neuro deficit, then paraplegia in coming days.
Recurrent infarctive wounds of feet from minor wheelchair trauma or pressure.
Lab: factor V Leiden, histology - diffuse thrombosis.

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

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




**67 F**

Acute skin necrosis.
*Suspicious history.*

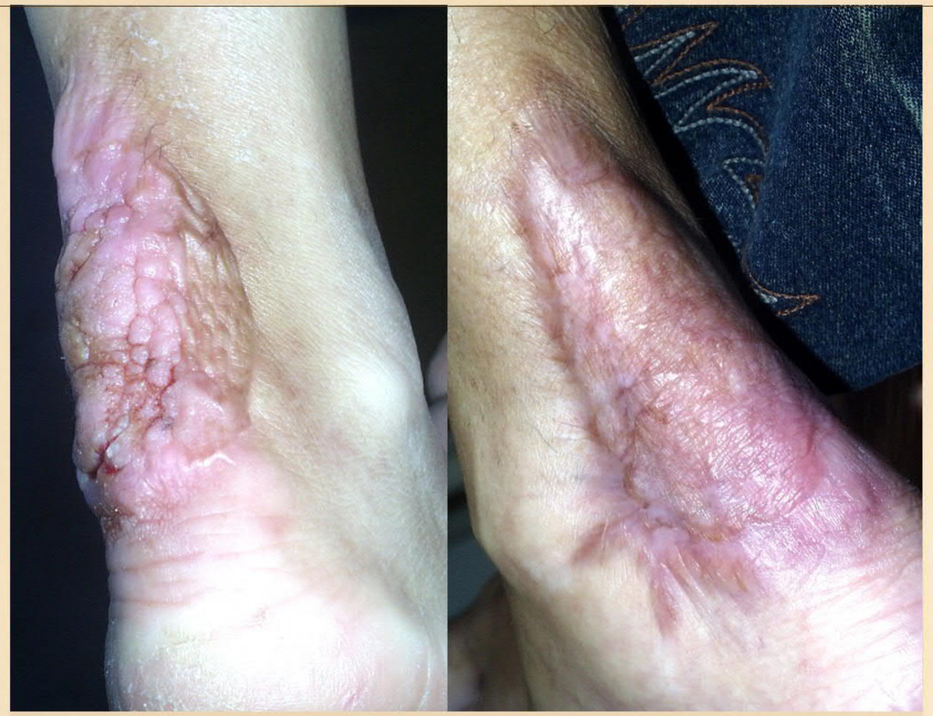
No prior risks or history.
Good pulses in feet.
*No other illness or explanation.*

Pure thrombo-infarctive pattern.
*Confirmatory exam.*

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

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

**Dx: Anti-thrombin-3 deficiency**



**44 F** **Dx: APL syndrome**

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

Otherwise healthy.
*No other illness or explanation.*

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

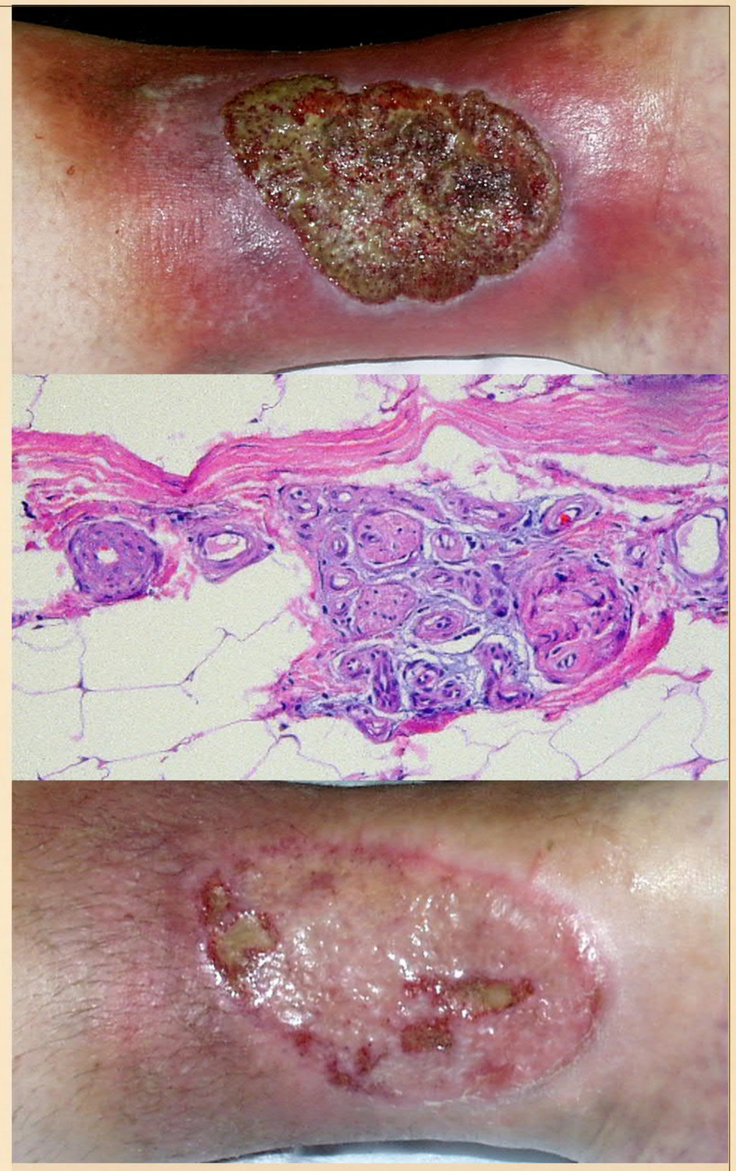
Healed: warfarin, hbo, biomatrix.
*Proper wound behavior only after warfarin.*

## The "hypercoagulable therapeutic triad".

**ANTICOAGULANTS**
**HYPERBARIC OXYGEN**
**REGENERATIVE BIOMATRICES**

**Each has its role to**

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



**30 F** **Dx: Mixed coagulopathy**

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

Wound surface "granulation tissue" infarcts.
*Confirmatory exam.*

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

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


"ALL IS VANITY"

# HYPERCOAGULABLE DISORDERS ARE COMMON

They are common disorders,
with broad clinical manifestations,
that can profoundly affect your patients,
without you knowing it.

But, they are under-appreciated and
frequently overlooked or misdiagnosed.

There is an historical basis for why they
are often missed, neglected, or discounted.

## Here is Why You Do Not Think of Them

*Even when they are all around you.*

---

### "All is Vanity"

*1892, by American illustrator Charles Allan Gilbert (1873 – 1929)*

It is a reminder that we may look but we might not see.
It reminds that we can fail to see that which later,
in retrospect then seems so obvious.

In the traditions of art and philosophy, it is also a
***memento mori***, a reminder of mortality.

Apropos of this subject, it reminds of the many patients who have suffered and even died due to failure to recognize and treat the hypercoagulable and micro-occlusive disorders.

FRANK LESLIE'S
# ILLUSTRATED
NEWSPAPER

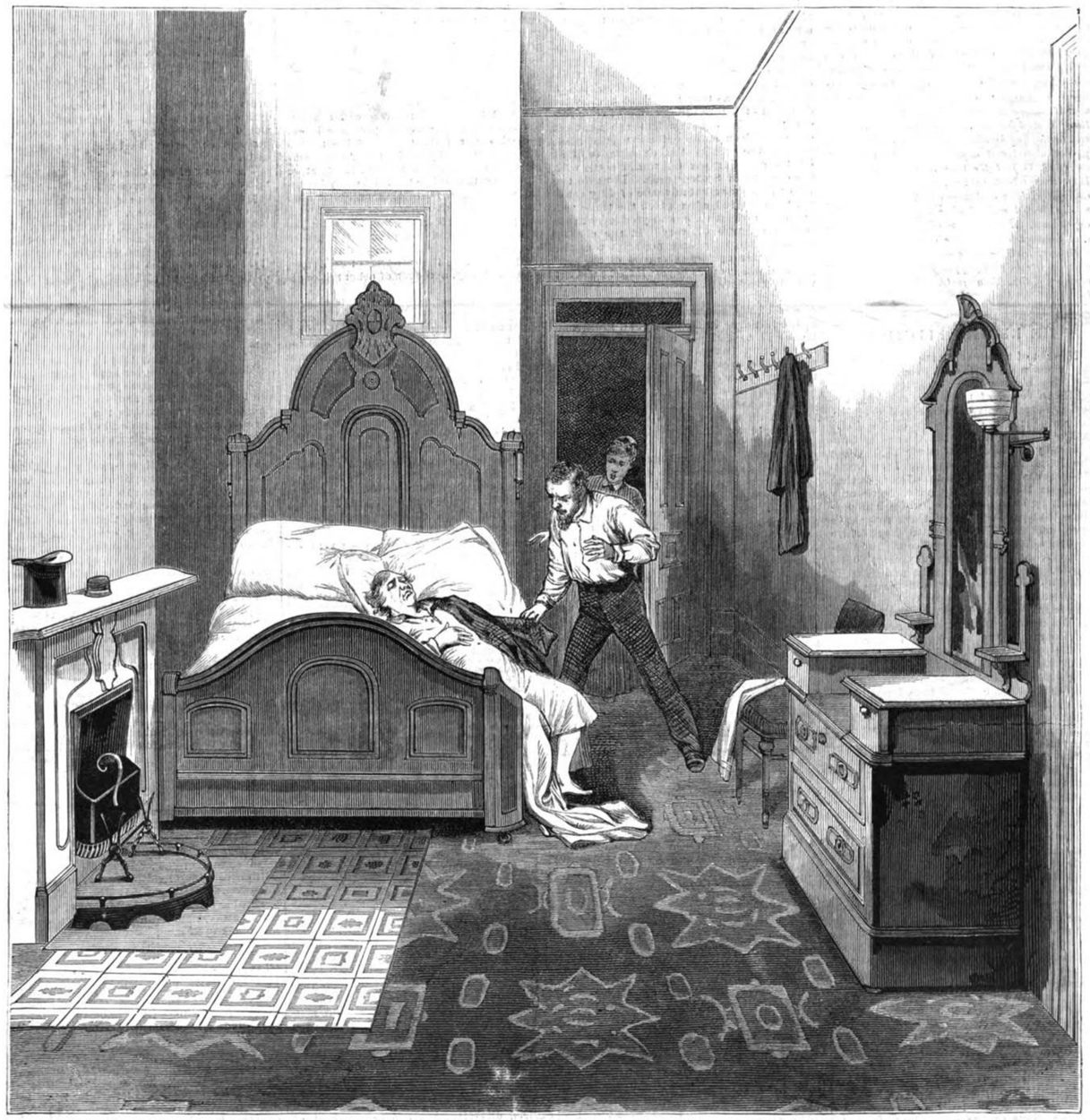
Entered according to the Act of Congress, in the year 1879, by FRANK LESLIE, in the Office of the Librarian of Congress at Washington.

No. 1,260—VOL. XLIX.] NEW YORK, NOVEMBER 22, 1879. [PRICE, WITH SUPPLEMENT, 10 CENTS. $4.00 YEARLY. 15 WEEKS $1.00.

## THE LATE HON. ZACHARIAH CHANDLER.

THE death of Hon. Zachariah Chandler, in the Grand Pacific Hotel at Chicago, created a profound sensation throughout the country. He had been filling a political campaign engagement, his last address being before an immense audience in McCormick's Hall, Chicago, on October 31st. Returning at the close with some friends to the hotel, he spent some time in conversation, during which he complained of an attack of indigestion. Although he had business requiring his attention at home on Saturday, he was persuaded to stop at the hotel over night, orders being given to call him at seven o'clock in the morning. When, on Saturday, the office-boy knocked upon the Senator's door there was no response; a second summons elicited no answer, and then the boy climbed to the transom and looked over. The body of the Senator was seen lying in an uneasy position on the bed—the feet extending over one side, his arms raised above his head and holding a coat that was partially wrapped about his shoulders. Gaining access to the bedroom, the boy found the Senator's body somewhat warm, but the pulse had ceased beating. Dr. McVickar was at once summoned, and he pronounced Mr. Chandler dead. From the arrangement of his clothing and the appearance of the room, it was surmised that he had awakened before the hour at which he was to have been called, and had laid out a clean shirt, having put the coat around his shoulders on account of the morning chill, and then, being stricken with apoplexy, had staggered towards the bed, and died in the position described.

(*Continued on page 203.*)



ILLINOIS.—THE LATE SENATOR ZACHARIAH CHANDLER—DISCOVERY OF THE DECEASED IN THE GRAND PALACE HOTEL, CHICAGO, NOVEMBER 1ST.
FROM A SKETCH BY ALBERT BERGHAUS.

**Zachariah T. Chandler**

1813-1879, businessman, ardent abolitionist, politician, mayor of Detroit 1851-52, a founder of the Republican Party, chair of RNC 1876-79, four-term senator from Michigan 1857-79, Secretary of the Interior under Ulysses S. Grant 1875-77.

***Died age 65, probably from a post-prandial myocardial infarction.***

***"Apoplexy"***

**Modern** - bleeding within, or arrest of blood flow with ischemic infarction, of an internal organ, and the accompanying symptoms, most commonly referring to a cerebrovascular event, a "stroke".

**Historical** - From 14th to the late 19th century, apoplexy referred to any sudden death that began with a sudden loss of consciousness, especially one when the victim died within moments of losing consciousness.

*Throughout those 500 years there was insufficient knowledge of internal organ pathology to understand the cause of stroke, heart attack, and other acute infarctions and sudden death.*

***Nathan Bailey 1730***

*APOPLEXY a Disease, which is a sudden Privation of all the Senses, and terrible Motions of the Body, those of the Heart and Lungs being excepted, and is attended with a Depravation of the principal Faculties of the Soul, by Reason that the Passages of the Brain are stopt, and the Course of the Animal Spirits hindered.*

***Samuel Johnson 1756***

*APOPLEXY. A sudden deprivation of all sensation. Locke.*

***Oxford English Dictionary 1888***

*Apoplexy. A malady, very sudden in its attack, which arrests more or less completely the powers of sense and motion; it is usually caused by an effusion of blood or serum in the brain, and preceded by giddiness, partial loss of muscular power, etc. Also applied by some to the effusion of blood in other organs.*

## THE LATE HON. ZACHARIAH CHANDLER.

The death of Hon. Zachariah Chandler, in the Grand Pacific Hotel at Chicago, created a profound sensation throughout the country. He had been filling a political campaign engagement, his last address being before an immense audience in McCormick's Hall, Chicago, on October 31st. **Returning at the close with some friends to the hotel, he spent some time in conversation, during which he complained of an attack of indigestion.** Although he had business requiring his attention at home on Saturday, he was persuaded to stop at the hotel over night, orders being given to call him at seven o'clock in the morning. When, on Saturday, the office boy knocked upon the Senator's door there was no response ; a second summons elicited no answer, and then the boy climbed to the transom and looked over. The body of the Senator was seen lying in an uneasy position on the bed – the feet extending over one side, his arms raised above his head and holding a coat that was partially wrapped about his shoulders. Gaining access to the bedroom, the boy found the Senator's body somewhat warm, but the pulse had ceased beating. Dr. McVickar was at once summoned, and he pronounced Mr. Chandler dead. From the arrangement of his clothing and the appearance of the room, it was surmised that he had awakened before the hour at which he was to have been called, and had laid out a clean shirt, having put the coat around his shoulders on account of the morning chill, **and then, being stricken with apoplexy, had staggered towards the bed, and died in the position described.**

# A HISTORY OF ANTICOAGULANT THERAPY

**Throughout history, blood was understood to clot, to "staunch" bleeding.**

**Every materia medica has agents to induce thrombosis, to control bleeding.**

Common Mugwort,
*Artemisia vulgaris*

## The Thornton Manuscript, circa 1450

**[F]or nosse bledyng.** For nosse bledyng, a remedy: Tak ele skynnes and dry þam & bryn þam & blaw þe powdir in his nose thirlles with a pipe.

## The Liber de Diversis Medicinis

## El Tabaco

Dr. Nicolas Monardes, 1569 & 1571
John Frampton 1577

***Joyfull newes out of the newe founde worlde***

**In reſtrainyng the flux of bloud of the wounds it doth moſt marveilous workes, for that the Joyce and the Leaves beyng ſtamped: is ſufficient to reſtraine any fluxe of bloud.**

# INTRA-VASCULAR THROMBOSIS

## IS A NON-OBVIOUS MODERN REVELATION

**Until that was realized, there was no need for therapeutic anticoagulation.**

### THE ADVENT OF ANTICOAGULANT THERAPY WAS CONTINGENT ON THREE DEVELOPMENTS

**– 1 –**

**Understanding that intravascular thrombosis is pathological and morbid.**

**– 2 –**

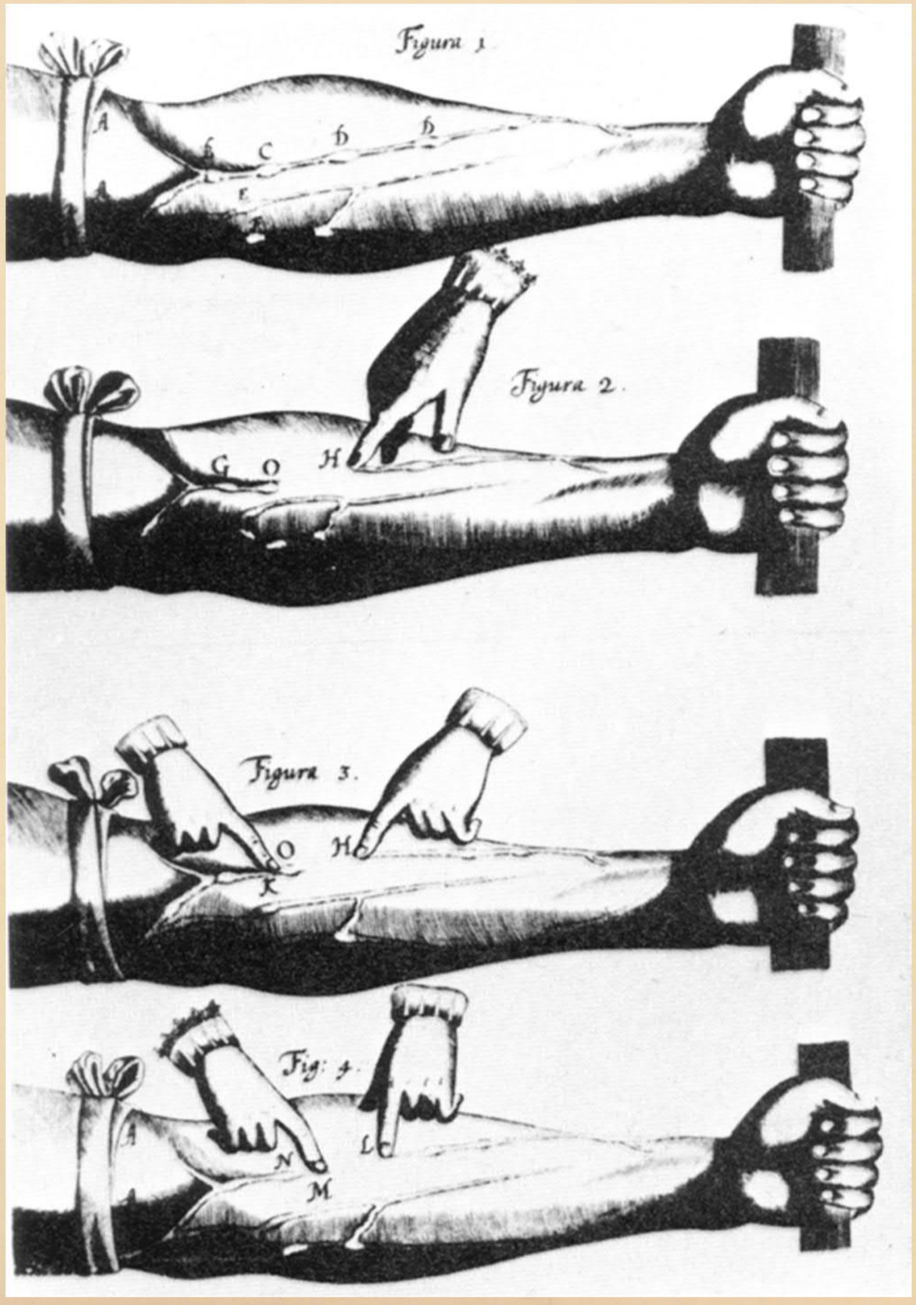
**Advances in medicine creating a need for anticoagulant therapies.**

**– 3 –**

**Finding and refining those therapies.**

Leonardo da Vinci, circa 1489-1513

William Harvey, 1628,
"De Motu Cordis"
Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus
*On the Movement of the Heart and Blood in Animals*



JO. BAPTISTÆ

# MORGAGNI

*P. P. P. P.*

## DE SEDIBUS ET CAUSIS

# MORBORUM

*PER ANATOMEN INDAGATIS*

LIBRI QUINQUE.

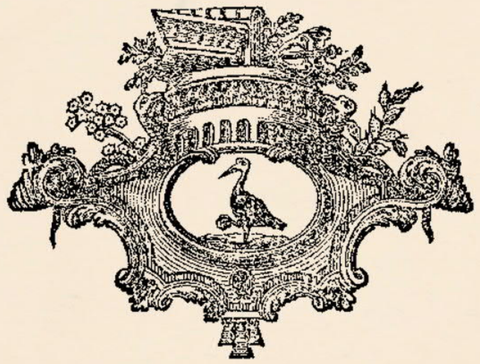
*DISSECTIONES, ET ANIMADVERSIONES, NUNC PRIMUM EDITAS, COMPLECTUNTUR PROPEMODUM INNUMERAS, MEDICIS, CHIRURGIS, ANATOMICIS PROFUTURAS.*

Multiplex præfixus eſt Index rerum, & nominum accuratiſſimus.

*Præfatus eſt S. A. D. TISSOT, M. D.*

TOMUS SECUNDUS,

EDITIO A MENDIS EXPURGATA ET AUCTA.



*EBRODUNI IN HELVETIA.*

M. DCC. LXXIX.

THE

# SEATS and CAUSES

OF

# DISEASES

INVESTIGATED BY ANATOMY,

## IN FIVE BOOKS,

CONTAINING

A Great Variety of DISSECTIONS, with REMARKS.

TO WHICH ARE ADDED

Very ACCURATE and COPIOUS INDEXES of the PRINCIPAL THINGS and NAMES therein contained.

TRANSLATED from the LATIN of

JOHN BAPTIST MORGAGNI,

Chief Profeſſor of Anatomy, and Preſident of the Univerſity at PADUA,

By BENJAMIN ALEXANDER, M. D.

IN THREE VOLUMES.

VOL. II.

LONDON,

Printed for A. MILLAR; and T. CADELL, his Succeſſor, in the Strand; and JOHNSON and PAYNE, in Pater-noſter Row.

MDCCLXIX.

**Giovanni Battista Morgagni,** 1682-1771

**1761**

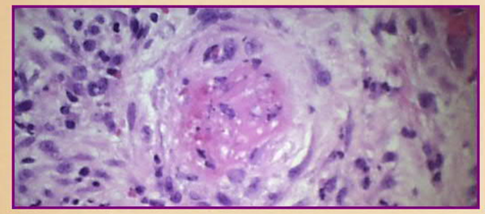
*De sedibus et causis morborum per anatomen indagatis*

**Benjamin Alexander, M.D.,** 1737-1768

**1769**

*The Seats and Causes of Diseases Investigated by Anatomy*

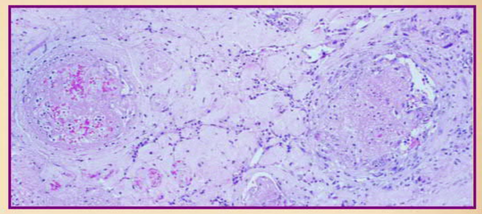
# The advent of anticoagulant therapy was contingent on three developments :



1 - Understanding that intravascular thrombosis is bad.

2 - Advances in medicine creating a need for anticoagulant therapies.

3 - Finding and refining those therapies.



## Rudolf Virchow, MD

1821 – 1901, Germany

**1856**

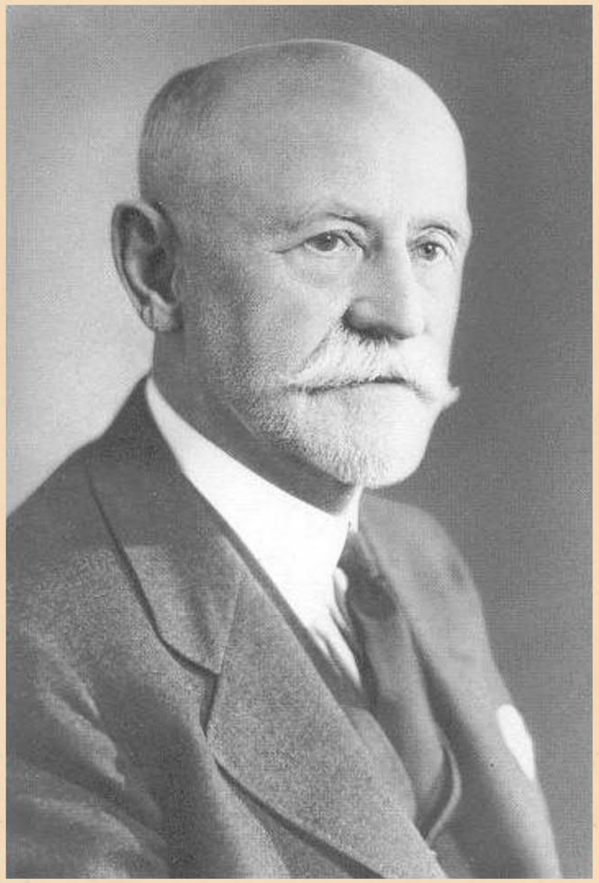
Venous Thromboembolism

### Virchow's Triad

*Blood stasis*

*Vascular injury*

*Hypercoagulability*



## James B. Herrick, MD

1861 – 1954, Chicago
Rush Medical College

**1910**

Herrick's Syndrome
(Sickle Cell Disease)

**1912**

Coronary Thrombosis
&
Myocardial Infarction


The Journal of the American Medical Association

Published Under the Auspices of the Board of Trustees

Vol. LIX, No. 23 — Chicago, Illinois — December 7, 1912


## CLINICAL FEATURES OF SUDDEN OBSTRUCTION OF THE CORONARY ARTERIES


JAMES B. HERRICK, M.D.
CHICAGO


Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident. Several events contributed toward the prevalence of the view that this condition was almost always suddenly fatal. Parry's writings on angina pectoris and its relation to coronary disease, Jenner's observations on the same condition centering about John Hunter's case, Thorvaldsen's tragic death in the theater in Copenhagen with the finding of a plugged coronary, sharply attracted attention to the relation between the coronary and sudden death. In Germany Cohnheim supported the views of Hyrtl and Henle as to lack of considerable anastomosis, and as late as 1881 lent the influence of his name to the doctrine that the coronary arteries were end-arteries; his Leipsic necropsy experience, as well as experiments on dogs, forced him to conclude that the sudden occlusion of one of these vessels or of one of the larger branches, such as the ramus descendens of the left coronary, meant death within a few minutes. Others emphasized the same view.

No one at all familiar with the clinical, pathologic or experimental features of cardiac disease can question the importance of the coronaries. The influence of sclerosis of these vessels in the way of producing anemic necrosis and fibrosis of the myocardium, with such possible results as aneurysm, rupture or dilatation of the heart, is well known. So also is the relation of the coronaries to many cases of angina pectoris, and to cardiac disturbances rather indefinitely classed as chronic myocarditis, cardiac irregularities, etc. It must be admitted, also, that the reputation of the descending branch of the left coronary as the artery of sudden death is not undeserved.

But there are reasons for believing that even large branches of the coronary arteries may be occluded — at times acutely occluded—without resulting death, at least without death in the immediate future. Even the main trunk may at times be obstructed and the patient live. It is the object of this paper to present a few facts along this line, and particularly to describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction.

Before presenting the clinical features of coronary obstruction, it may be well to consider certain facts that go to prove that sudden obstruction is not necessarily fatal. Such proof is afforded by a study of the anatomy of the normal as well as of the diseased heart, by animal experiment and by bedside experience.

The coronaries are not so strictly end-arteries, i. e., with merely capillary anastomoses, as Cohnheim and others thought. By careful dissections, by injection of one artery from another, by skiagraphs of injected arteries and by direct inspection of hearts made translucent by special methods, there is proof of an anatomic anastomosis that is by no means negligible.

Jamin and Merkel's† beautiful stereoscopic skiagrams show the remarkably rich blood-supply of the heart, with occasional anastomoses between vessels of considerable size. The possibility of injection of one coronary artery from the other is admitted even by those who deny that such injection proves more than a capillary non-functioning anastomosis. Amenomiya,[1] by injecting hearts of young persons, showed naked-eye anastomoses in the subepicardial tissue. He feels that Hirsch and Spaltholz[2] have nearly cleared up the question as to the relation between the heart muscle and disease of the coronary artery from the anatomic standpoint. Hirsch says that in dogs the anastomosing vessels are functionally competent, and Spaltholz says that in man the vessels are nearly the same as in dogs, rich in anastomoses even in those of considerable caliber. The latter investigator, by a method of injection and treatment of the heart so as to make the muscle transparent, shows to the naked eye that there are anastomoses of considerable size.

Among others who are on record as believing that there are non-negligible anastomoses may be mentioned Haller, Huchard, Orth, Michaelis, Langer, Legg, West. All recognize, however, that there are individual differences, and also that though the heart may show rich anastomoses, these are not necessarily functional, i. e., that an artery which anatomically is not a terminal artery may yet be such functionally.

But there is proof not only of anatomic connection between the two coronaries, but that in certain instances, at least, such connection is of functional value. Experiments on lower animals and the clinical experiment of disease of the coronaries with autopsy findings show this.

Much of the earlier experimental work on the lower animals, obstructing the coronary arteries by ligatures, clamps or artificial emboli, gave promptly fatal result. Among those who worked along this line and reached these conclusions may be mentioned Erichsen (1842), Panum (1862), von Bezold, Samuelson (1880), Cohn-

† Jamin and Merkel: Die Koronararterien des menschlichen Herzens in stereoskopischen Röntgenbildern, Jena, 1907. Extensive bibliographies are contained in the articles by Thorel (Lubarsch-Ostertag's Ergebnisse, ix, Abt 1), and in Amenomiya (Virchows Arch. f. path. Anat., 1910, cxcix, 187). I repeat only some of the more important references and add new ones.

1. Amenomiya: Ueber die Beziehungen zwischen Koronararterien und Papillarmuskeln im Herzen, Virchows Arch. f. path. Anat., 1910, cxcix, 187.

2. Hirsch and Spaltholz: Koronararterien und Herzmuskel, Deutsch. med. Wchnschr., 1907, No. 29.

**The advent of anticoagulant therapy was contingent on three developments :**

1 - Understanding that intravascular thrombosis is bad.

2 - Advances in medicine creating a need for anticoagulant therapies.

3 - Finding and refining those therapies.

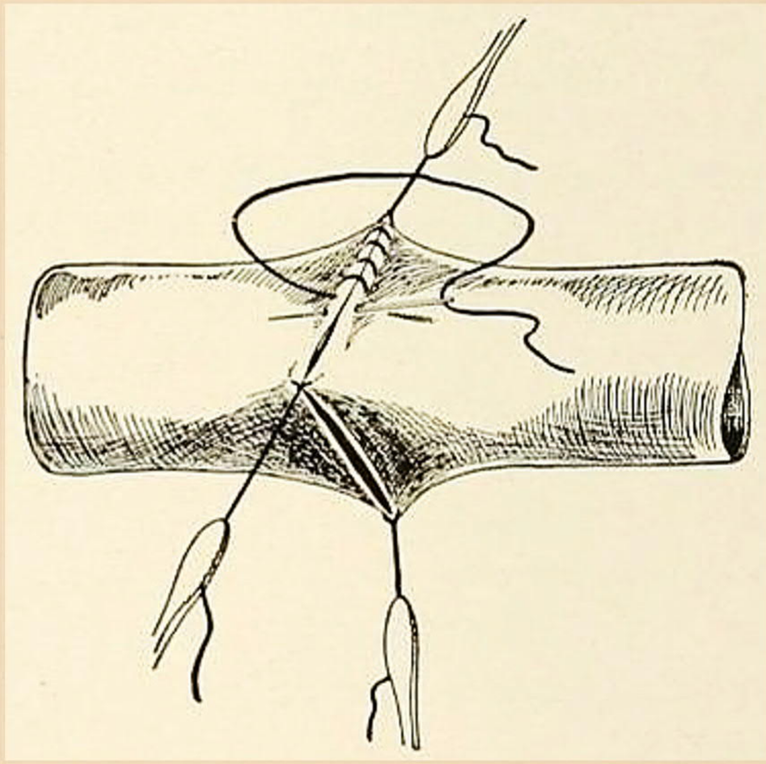
## Hieronymous Brunschwig

1450 – c1512

1497

Das buch
der Cirurgia,
Hantwirckung der
wundartzny.

*The book of Surgery,*
*treatment of the*
*wound.*



## Alexis Carrel

1873 – 1944

1902

*Carrel A. and Morel B.*
*Anastomose bout a bout de la jugulaire*
*et de la carotide primitive.*
*Lyon Medical 1902; 99:114-6.*

Nobel Prize
1912

# The advent of anticoagulant therapy was contingent on 3 developments :

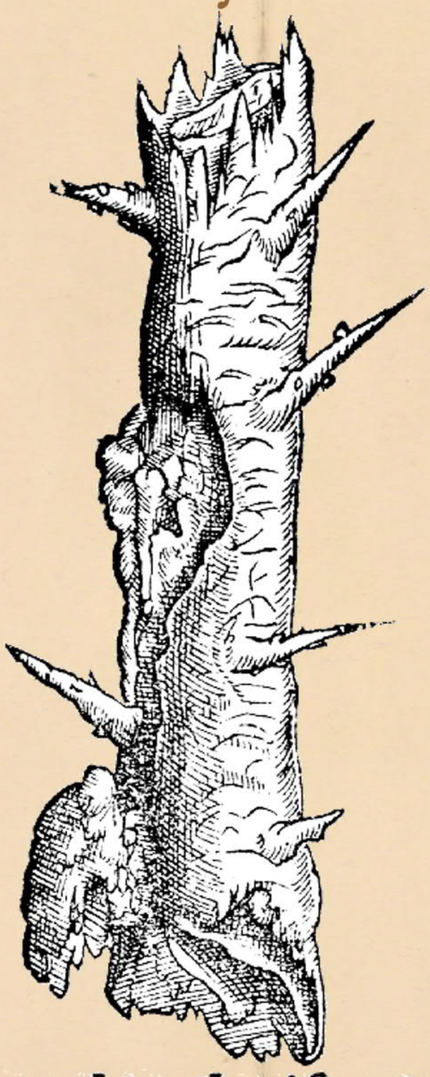
1 - Understanding that intravascular thrombosis is bad.

2 - Advances in medicine creating a need for anticoagulant therapies.

3 - Finding and refining those therapies.


Patent medicine,
*trade card* c 1885

John Gerard, 1597
Thomas Johnson, 1633
*The Herball or Generall Historie of Plantes*

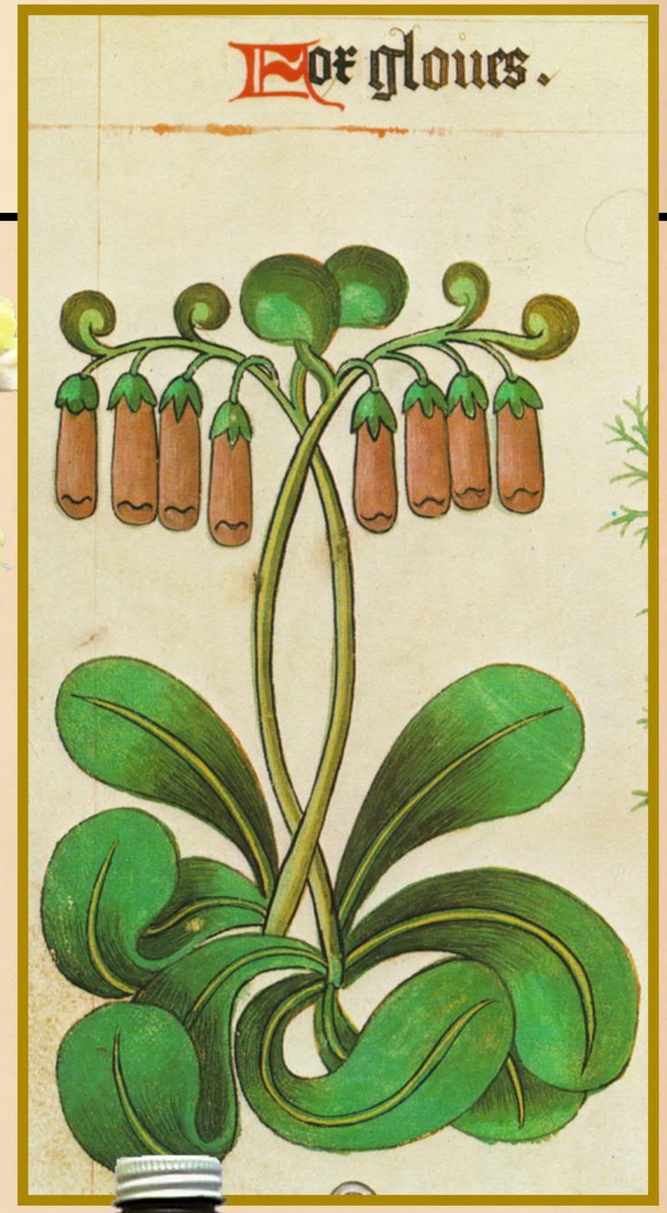


*Arbor Thurifera.*
The Frankincenſe tree.

• • •

filleth vp hollow vlcers,
it cloſes raw wounds

Common mullein *Verbascum thapsus*




England,
c 1510

*Herbal and Bestiary*


Compounded medicinals


Making Dr. Brown's Cough Balsam, Milwaukee, Wisconsin, *1896*

Acetylsalicylic acid, Bayer, *(founded 1863)* Germany, *1897*


The Norwich Pharmacal Company,
*(founded 1887)* Norwich, New York
*early 1900's*

# Heparin

**Charles Best** (1899-1978) & Frederick Banting (1891-1941), **1921**
***Purification of heparin 1929-1937.*** >> {Crafoord, DVT, Acta, 1937}

*Unidentified lab student, Johns Hopkins Medical School, c 1915*

**Jay McLean** (1890-1957) & **William Howell** (1860-1945) : *heparin 1916*

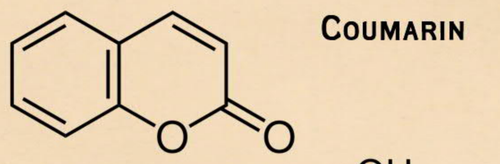
*Sweet Clover, Melilotus officinalis*

John Gerard, 1597 Thomas Johnson, 1633

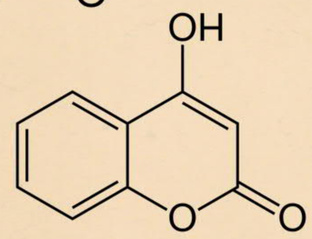
*The Herball or Generall Historie of Plantes*

With the juice hereof . . . is made a moſt ſoueraigne healing and drawing emplaſter . . . made by a skilfull Surgion.

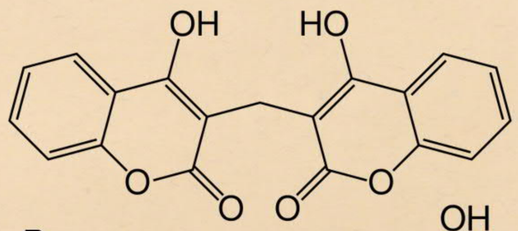
# Coumarin and the Dicoumarol Derivatives



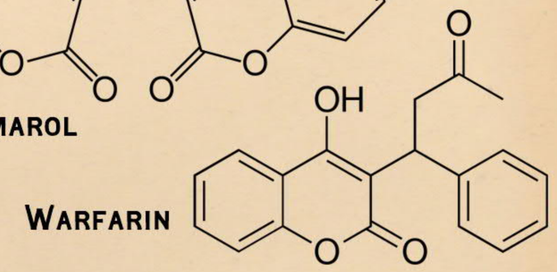

COUMARIN




4-HYDROXY COUMARIN




DICOUMAROL




WARFARIN

## Warfarin

# Anticoagulants

## Measuring Effect and Monitoring Therapy

**Problematic pharmacokinetics**
**Narrow therapeutic index**
**Goldilocks dose**

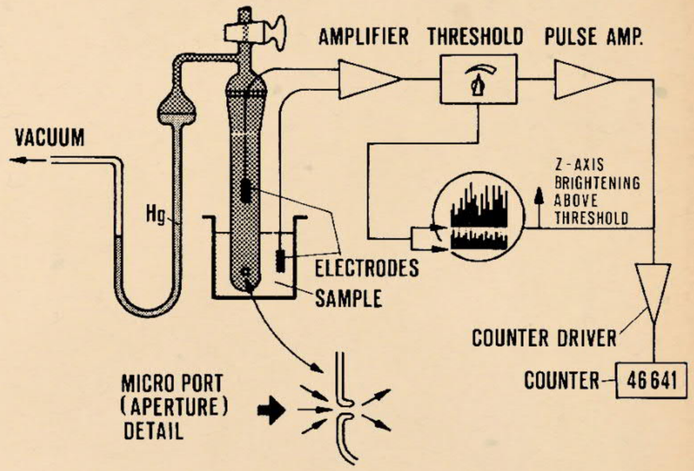
**MATULA DISK**
Udalricus Binder, 1506
*Epiphaniae medicorum,*
*Speculum videndi urinas hominum*

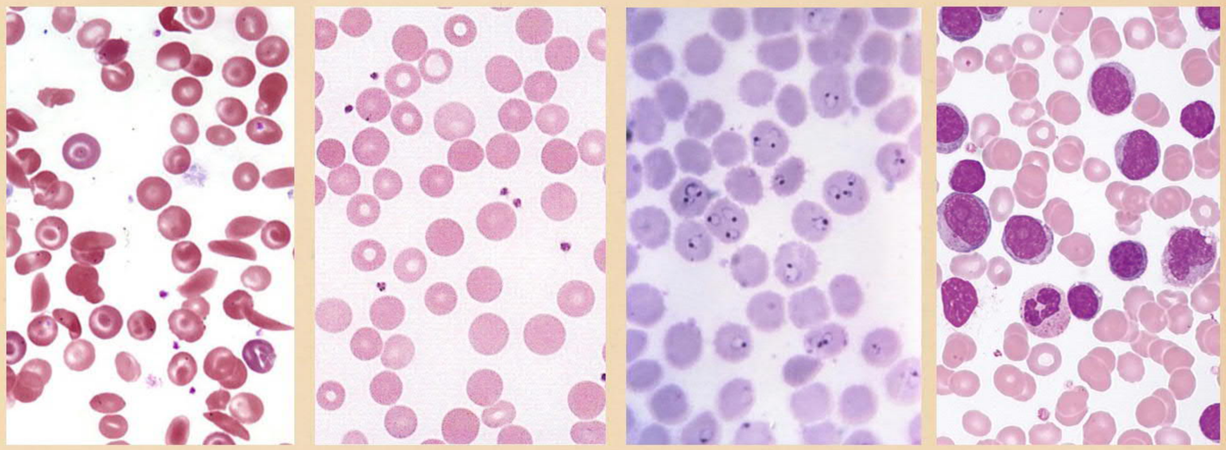
# TECHNOLOGY:

To discover the Rx.

To produce the Rx.

To monitor the Rx.

*Herrick's / sickle* *spherocytosis* *malaria* *AML leukemia*

PATIENT INFORMATION

REPORT STATUS: FINAL

SPECIMEN INFORMATION
SPECIMEN:
REQUISITION:
LAB REF NO:

COLLECTED:
RECEIVED:
REPORTED:

DOB:
AGE:
GENDER:
FASTING:

Clinical Info:

ORDERING PHYSICIAN

CLIENT INFORMATION

ACCESA LABS
Order Today
www.accesalabs.com/arthritis

| Test Name | Result | Flag | Reference Range | Lab |
|---|---|---|---|---|
| FASTING: UNKNOWN | | | | |
| **URIC ACID** | | | | |
| URIC ACID | 9.5 | HIGH | 4.0-8.0 mg/dL | 01 |
| Therapeutic target for gout patients: <6.0 mg/dL | | | | |

# The Hypercoagulable Disorders - First Light



employment the occupational medical officer should also be notified.

Few diabetics register on the Disabled Persons Register, but those with disabling complications may find it advantageous to do so and to seek the advice of their local disablement resettlement officer.

The present positive attitude towards the management of diabetes has ensured that most diabetics can be usefully and suitably employed, but the satisfactory care of the diabetic employee does require efficient medical support with good co-operation between the diabetic clinic, the family physician, and the occupational health service.

JOHN LITTLER

Consultant Physician,
East Berkshire Health District,
Windsor SL4 3AG

1 Lister J. The environment of diabetes. *Journal of Social and Occupational Medicine* 1982;32:153-5.
2 Jackson JGL, British Diabetic Association employment survey. London: British Diabetic Association, 1981.
3 Frier BM, Steel JM, Matthews DM, Steel JM, Dornhorst LJP. Driving and insulin-dependent diabetes. *Lancet* 1980;i:1233-4.
4 Matthaeus L, Tyrrell J, Alexander WW. Physician's guidelines for employment and placement of the diabetic in industry—an update. *JOM* 1980;22:505-7.
5 Szabo S. Diabetes—its relation to industry. *Industrial Medicine and Surgery* 1954;23:108-9.

## Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

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

The serological abnormality common to some (but not all) of these patients is a circulating anticardiolipin antibody responsible for the positive Wassermann reaction or so called false positive serological test for syphilis. Over 25 years ago Laurell and Nilsson[2] recognised that patients with systemic lupus erythematosus with biological false positive Wassermann reactions also had a high incidence of another "antilipid" antibody—the so called "lupus anticoagulant." This antibody, now known to be present in conditions other than systemic lupus erythematosus, appears to act by interfering with the binding of phospholipid to form prothrombin activator, thereby affecting both the intrinsic and extrinsic clotting pathways.[3] Though in laboratory tests the lupus anticoagulant slightly prolongs the partial thromboplastin time, the seeming paradox is that its presence in a patient's circulation appears to be associated not with bleeding but with a tendency to thrombosis.[4, 5]

Mueh *et al* reviewed 35 patients whose plasma possessed lupus anticoagulant activity. Six of these patients had systemic lupus erythematosus, and 24 had autoimmune abnormalities.[6] Six of 28 patients had a positive Venereal Disease Research Laboratory test result. Eleven of the 35 patients suffered one or more thrombotic episodes, including cerebral thrombosis. Six of the patients had thrombocytopenia (possibly due to antibody activity against phospholipid antigen in the platelet membrane).

Another clinical association subsequently observed in association with the lupus anticoagulant is recurrent spontaneous abortion.[7] Our mechanism for this was suggested by Carreras *et al*,[7] who studied a patient with recurrent arterial thrombosis and intrauterine fetal death. The IgG fraction of her serum containing lupus anticoagulant was found to inhibit the production of prostacyclin ($PGI_2$) by rat aorta and pregnant myometrium. They speculated that by its effect on phospholipids the lupus anticoagulant might interfere with the release of arachidonic acid from the cell membranes.

Recent studies from the Hammersmith Hospital have confirmed and extended the association of the lupus anticoagulant with thrombosis. Boey *et al* studied 31 patients with systemic lupus erythematosus and other connective tissue diseases whose plasma showed lupus anticoagulant activity.[9] Thrombotic episodes such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, and axillary vein thrombosis were recorded in 18 of the 31. Of the 26 women with lupus anticoagulant activity, nine gave a history of one or more abortions. Seven of the 31 patients had positive Venereal Disease Research Laboratory test results. Asherson *et al*[10] from the same unit reported six patients with systemic lupus erythematosus and pulmonary hypertension, five of whom had lupus anticoagulant activity—a finding that stimulates speculation on a possible wider role of lupus anticoagulant in "idiopathic" pulmonary hypertension, where serological abnormalities including false positive serological tests for syphilis have been previously observed, and where intrapulmonary venous thrombosis may be a contributing factor. Further interesting anecdotal observations from these studies were the association of antinuclear antibody negative discoid lupus erythematosus with the lupus anticoagulant and pulmonary hypertension[10] and the association of the lupus anticoagulant with "idiopathic" portal hypertension in one patient and with renal vein thrombosis in two others.

Elegant studies supporting the concept that some antibodies may cross react with complex lipid antigens have been reported by Stollar, Schwartz, and others, who showed that monoclonal anti-DNA antibodies, raised from lupus mice, may bind a variety of polynucleotides and phospholipids.[11–13] One such antibody also had lupus anticoagulant activity. In such antibodies the antigenic determinants appeared to be the phosphodiester linked phosphate group present in some phospholipids, including cardiolipin, as well as in the sugar phosphate backbone of polynucleotides such as DNA.[11–13] Certain restricted groups of lymphocytes may produce antibodies with idiotypic diversity. Of interest is the report that immunisation of normal rabbits or mice with cardiolipin stimulates the production of both anticardiolipin and anti-DNA antibodies.[13]

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

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

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

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

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

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

GRAHAM R V HUGHES

Consultant Physician,
Hammersmith Hospital,
London W12 0HS

1 Colaco CH, Elkon KB, Gharavi AE, Hughes GRV. The lupus anticoagulant: clinical and laboratory associations. (Abstract.) *Ann Rheum Dis* 1983;**42**:228.
2 Laurell B-B, Nilsson IM. Hypergammaglobulinemia, circulating anticoagulant, and biologic false positive Wassermann reaction. *J Lab Clin Med* 1957;**49**:694-707.
3 Byron MA. The clotting defect in SLE. *Clin Rheum Dis* 1982;**8**:137-51.
4 Bowie EJW, Thompson JH Jr, Pascuzzi CA, Owen CA Jr. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. *J Lab Clin Med* 1963;**62**:416-30.
5 Firkin BG, Howard MA, Radford N. Possible relationship between lupus inhibitor and recurrent abortion in young women. *Lancet* 1980;ii:366.
6 Manoharan A, Gibson L, Ruth B, Feery BJ. Recurrent venous thrombosis with a "lupus" coagulation inhibitor in the absence of systemic lupus. *Aust NZ J Med* 1977;**7**:422-6.
7 Carreras LO, Defreyn G, Machins SJ, *et al*. Arterial thrombosis, intrauterine death and "lupus" anticoagulant: detection of immunoglobulin interfering with prostacyclin formation. *Lancet* 1981;i:244-6.
8 Mueh JR, Herbst KD, Rapaport SI. Thrombosis in patients with the lupus anticoagulant. *Ann Intern Med* 1980;**92**:156-9.
9 Boey ML, Colaco CB, Gharavi AE, Elkon KB, Loizou S, Hughes GRV. Thrombosis in SLE: striking association with the presence of circulating lupus anticoagulant. *Br Med J* 1983;**287**:1021-3.
10 Asherson RA, Mackworth-Young CG, Boey ML, *et al*. Pulmonary hypertension in systemic lupus erythematosus. *Br Med J* 1983;**287**:1024-5.
11 Lafer EM, Rauch J, Andrzejewski C Jr, *et al*. Polyspecific monoclonal lupus autoantibodies reactive with both polynucleotides and phospholipids. *J Exp Med* 1981;**153**:897-909.
12 Shoenfeld Y, Rauch J, Massicotte H, *et al*. Polyspecificity of monoclonal lupus autoantibodies produced by human-human hybridomas. *N Engl J Med* 1982;**308**:414-20.
13 Schwartz RS. Monoclonal lupus autoantibodies. *Immunology Today* 1983;**4**:68-9.
14 Lubbe WF, Butler WS, Palmer SJ, Liggins GC. Fetal survival after prednisone suppression of maternal lupus-anticoagulant. *Lancet* 1983;i:1461-2.
15 Harris EN, Gharavi AE, Boey ML, *et al*. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in SLE. *Lancet* (in press).
16 Wilson WA, Hughes GRV. Aetiology of Jamaican neuropathy. *Lancet* 1975;i:345.
17 Hughes GRV. Central nervous system lupus—diagnosis and treatment. *J Rheumatol* 1980;**7**:405-11.

## Malaria vaccination: two steps forward, one backward

In the two years since the topic of malaria vaccination was last reviewed in the *BMJ*[1] important technical advances have been made in the search for antigens that can induce a protective response against the various stages of the malaria parasite. The pertinent question is whether, or to what degree, these advances bring us closer to the manufacture and practical deployment of a vaccine to protect people against this disease.

Without question multiple drug resistance in the malignant tertian parasite, *Plasmodium falciparum*, is spreading alarmingly across the eastern parts of the African continent and Madagascar. Resistance is also extending westwards across India and eastwards as far as malaria goes in the south west Pacific. The endemic areas of Latin America, too, have faced this problem for many years. Radically new antimalarial drugs are most unlikely to become available in the short term, especially for prophylaxis. Reports on mefloquine, a potent, synthetic analogue of quinine, are already throwing up hints that parasites can become resistant to it, even though the drug is still only in the stage of clinical trial. Artemisinine (Qinghaosu), the new derivative of an ancient Chinese herbal remedy, is at an early stage of its development and looks likely to lend itself only to therapeutic and not to prophylactic use. Other new drugs such as halofantrine (in a sense an analogue of mefloquine) and a new series of quinones which are the subject of patent applications by the Wellcome Foundation will need at least five more years of investigation before they could be widely applied even if they overcome all the hurdles of new drug development. No new insecticides are on the horizon that are both technically superior to DDT and economically deployable by most Third World countries. Inevitably, therefore, great hopes are being pinned on the malaria vaccines as

## Antiphospholipid Antibody Syndrome: A New Cause of Nonhealing Skin Ulcers

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

*Chicago, Ill.*

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

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

### Case Report

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

On admission, the lesions were noted to be erythematous, purple, macular lesions with central, shallow ulcerations that tended to coalesce (Fig. 1). The ulcers, as well as some smaller satellite lesions, were located predominantly in the lower medial pretibial region. There were multiple, small depressed scars about the leg and small regions of hyperpigmentation

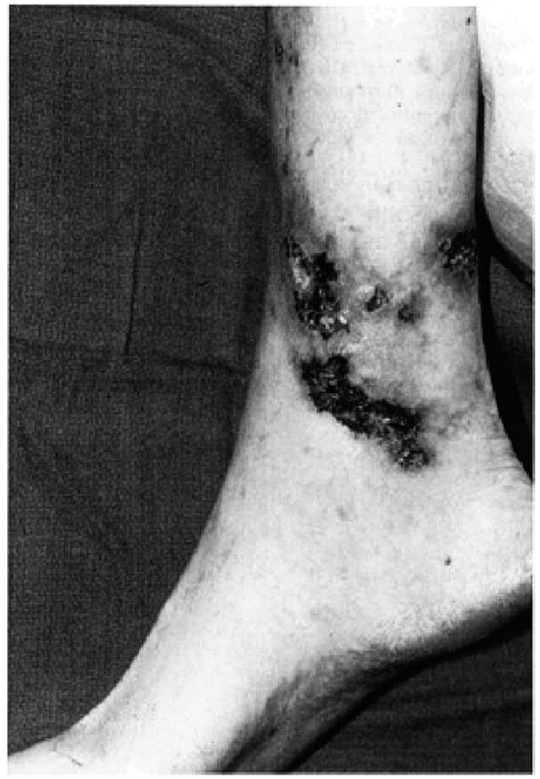


Fig. 1. Photograph of patient's right leg at presentation. Note the erythematous, macular lesions with shallow, central ulcerations.

over the entire thigh and leg. The ulcerated areas were profoundly tender to touch. The skin of the foot was warm and well perfused, and pedal pulses were palpable. Significant laboratory results included mildly elevated white blood cell count and erythrocyte sedimentation rate, a positive lupus-like anticoagulant, and elevated cardiolipin antibodies. Arterial Doppler studies were normal. Arteriography revealed

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



## Thrombosis, abortion, cerebral disease, and the lupus anticoagulant

*Graham RV Hughes, British Medical Journal 1983*

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

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



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

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

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

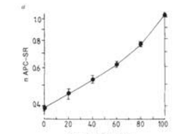
Activated protein C (APC) is a serine protease with potent anticoagulant properties, which is formed in blood on the endothelium from an inactive precursor[1]. During normal haemostasis, APC limits clot formation by proteolytic inactivation of factors Va and VIIIa (ref. 2). To do this efficiently the enzyme needs a non-enzymatic cofactor, protein S (ref. 3). Recently it was found that the anticoagulant response to APC (APC resistance)[4] was very weak in the plasma of 21% of unselected consecutive patients with thrombosis[5] and about 50% of selected patients with a personal or family history of thrombosis[6,7]; moreover, 5% of healthy individuals show APC resistance, which is associated with a sevenfold increase in the risk for deep vein thrombosis[8]. Here we demonstrate that the phenotype of APC resistance is associated with heterozygosity or homozygosity for a single point mutation in the factor V gene (at nucleotide position 1,691, G→A substitution) which predicts the synthesis of a factor V molecule (FV Q506, or FV Leiden) that is not properly inactivated by APC. The allelic frequency of the mutation in the Dutch population is ~2% and is at least tenfold higher than that of all other known genetic risk factors for thrombosis (protein C (ref. 8), protein S (ref. 9), antithrombin[10] deficiency) together.

The responsiveness of plasma to APC is measured as the ratio of two activated partial thromboplastin times, one in the presence of APC and one in its absence[4,5,7]. This APC-sensitivity ratio (APC-SR) is normalized to the ratio obtained with a reference plasma (n-APC-SR). Resistance to APC is defined by a n-APC-SR <0.84 (1.96 s.d. below the mean n-APC-SR in 100 healthy controls, after outlier removal).

Analysis of the parentships of 14 unrelated APC-resistant patients led to the concept of a familial form of APC resistance (or deficiency of APC cofactor II[8]) in which homozygotes and heterozygotes can be identified on the basis of the n-APC-SR (Fig. 1 legend). Further support for this came from mixing equal volumes of normal plasma and plasma from a patient classified as homozygous cofactor II-deficient (n-APC-SR, 0.38), which gave a n-APC-SR of 0.57 (Fig. 1a). This is identical to the ratio for plasma from patients heterozygous for the deficiency (mean n-APC-SR, 0.58). Mixing the plasma of four unrelated homozygous APC cofactor II-deficient patients (mean n-APC-SR, 0.40) did not alter the ratio, indicating that in all four patients the same plasma protein was missing or defective (see also refs 4 and 7).

To investigate whether APC cofactor II activity is a feature of one of the known blood coagulation proteins, APC cofactor II was assayed in a series of plasmas deficient in a single protein (Fig. 1b). All contained normal levels of APC cofactor II (60–155%) apart from plasma deficient in factor V (<5%). Addition of isolated human factor V to factor V-deficient plasma introduced factor V coagulant activity and APC cofactor II activity, suggesting that the latter is related to factor V (see also ref. 11).

Independent support for the identity of factor V with APC cofactor II came from linkage studies in a large family with APC resistance (Fig. 2a). The human locus for the factor V gene (*F5*) has been mapped to chromosome 1 (1q21–25)[12]. There are no reports of polymorphic *F5* markers[13,14] that can be amplified by polymerase chain reaction (PCR). Therefore, we tested the



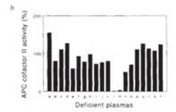




FIG. 1 Measurement of APC-cofactor II levels in plasma. a, Calibration curve for the assay of APC-cofactor II activity in plasma. APC cofactor II refers to the hypothetical new cofactor of APC[4] which is missing or defective in individuals with APC resistance. n-APC-SRs were measured in dilutions of normal plasma (100% APC cofactor II) in plasma of a patient homozygous-deficient in APC cofactor II (0% APC cofactor II). The curve in a is the result of nine different experiments. The classification as homozygous- or heterozygous-deficient in APC cofactor II is based on the results of parentship analysis for 14 probands with APC resistance (n-APC-SR <0.84). For 2 probands (n-APC-SR, 0.38/0.41), both parents were APC resistant (mean n-APC-SR 0.55); for 11 probands (mean n-APC-SR 0.57) one of the parents was APC resistant (mean n-APC-SR 0.59) whereas the other was not (mean n-APC-SR 0.96); for one proband (n-APC-SR 0.74), neither parent was affected (n-APC-SR 0.96/0.99). We propose that individuals can be classified as homozygotes or heterozygotes for APC cofactor II deficiency on the basis of their n-APC-SR (homozygotes: mean 0.40, $n = 2$; heterozygotes: mean 0.58, range 0.51–0.67, $n = 26$). b, APC cofactor II activity levels in plasmas deficient (<5%) in a single coagulation factor. Plasmas were either from patients with a congenital deficiency (a, g, f, m, g, r, s, t) or prepared by immunodepletion (b, c, d, e, j, h, i, k, l, p). Plasmas were deficient in factor II (a), factor VII (b), factor IX (c), factor X (d), factor XI (e), factor XII (j), factor XIII (g), protein C (i), protein S (o), β2-glycoprotein (j), antithrombin (k), factor V (l, m), factor VIII (p, q) or von Willebrand factor (r, s, t). Factor V-deficient plasma (m) was supplemented with two different concentrations, 54% (n) and 90% (o), of purified human factor V (Serbio, Gennevilliers, France), dialysed against 20 mM sodium citrate, 150 mM NaCl, 4 mM $CaCl_2$, and tested for APC cofactor II activity. METHODS. The APC-SR was calculated from the results of two activated partial thromboplastin times, one measured in the presence of APC and one in its absence, as before[4]. The n-APC-SR was calculated by dividing the APC-SR for the test sample by the APC-SR for pooled normal plasma. APC cofactor II activity was measured by reading the n-APC-SR for two different dilutions (1:1, 3:4) of the test plasma in APC cofactor II-deficient plasma on a calibration curve as shown in a.



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

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

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

## Factor V Leiden

*Bertina RM (Leiden, the Netherlands)*
*Nature 1994*

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

*Plastic and Reconstructive Surgery: April 1995*

**This author-presenter's first exposure to the hypercoagulable disorders.**

*The seed from which this presentation has blossomed.*


# Timeline of Understanding that Intravascular Thrombosis Occurs

1761 Morgagni – premortem intra-vascular thrombosis observed but not understood

## Cognition, concepts, pathology

1856 Virchow – physiology & pathology

1912 Herrick - disease

1912 Carrel - technique

## Therapy & clinical integration

1916 McLean et al – heparin discovered

1930 Best et al - clinical heparin

1937 Crafoord - heparin in service

## Progressive tools & Rx options

1920 Sweet clover disease

1940 Dicoumarol

1950 Current clinical concepts established
*indications, drugs, methods*

## Mainstreaming patient care

1957 Coulter, Auto-Analyzer
*lab makes Rx practical*

## Modern practice

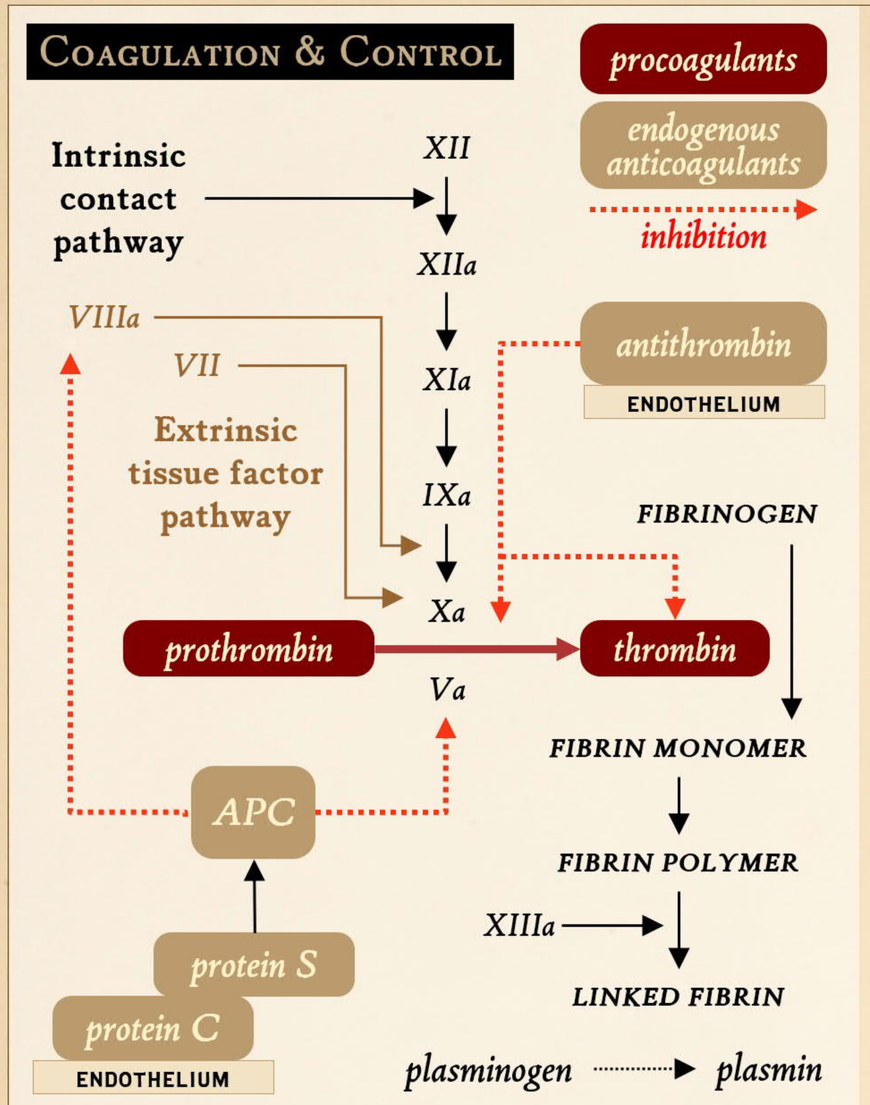
1960 expanded applications
*vascular & heart surgery, microsurgery, vascular implants, dialysis, catheters, transplantation and replantation*

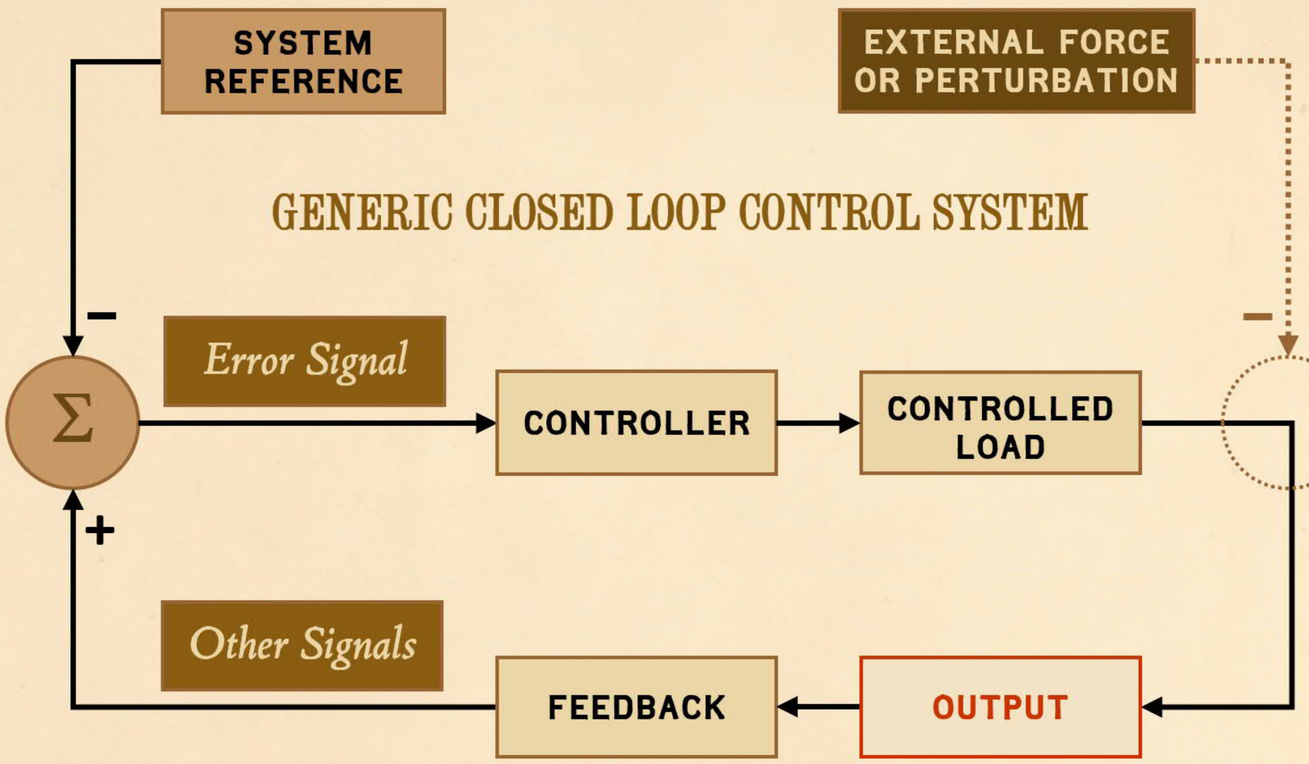
1990 hypercoagulable disorders

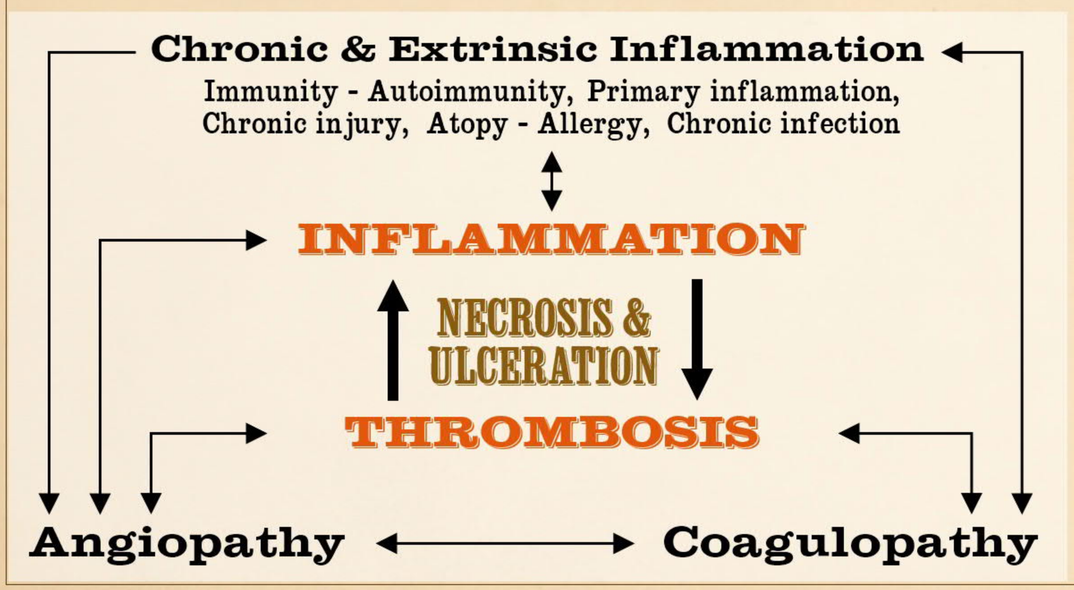
2000 new pharmaceuticals (*LMW-hep, DTI's*)

# THE PHYSICS OF COAGULATION & THROMBOSIS

## A Non-Linear Multi-Control System



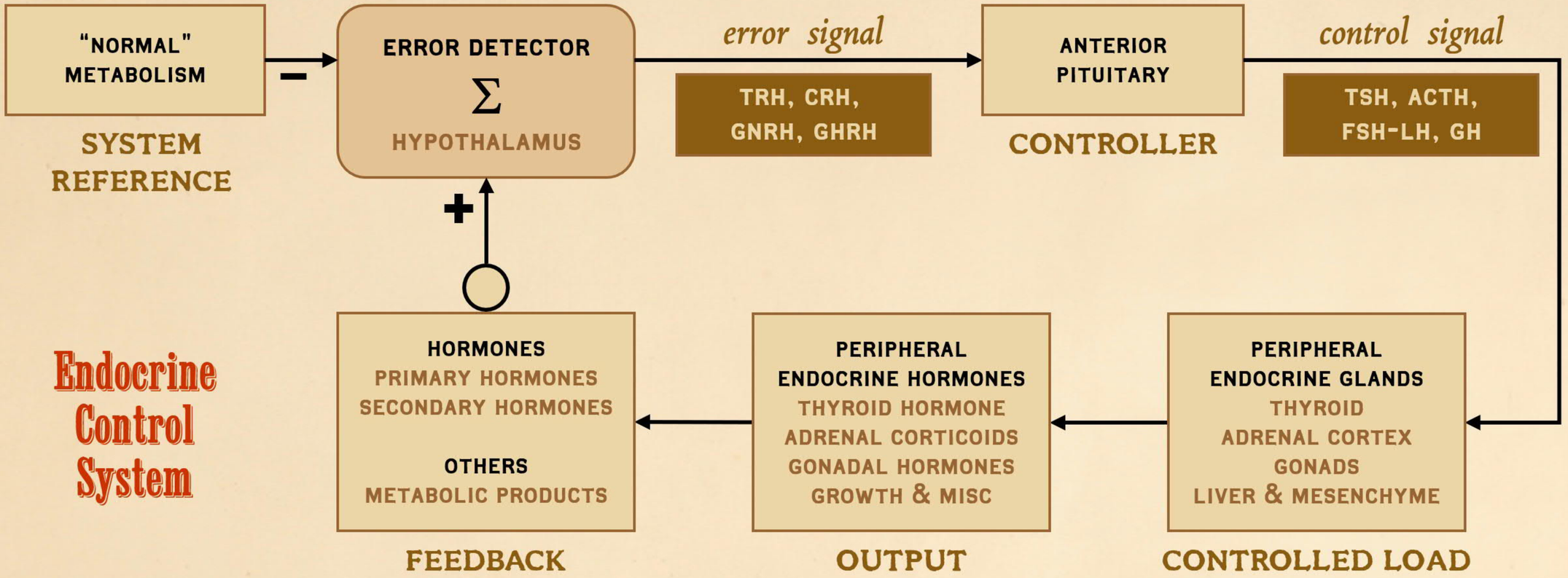



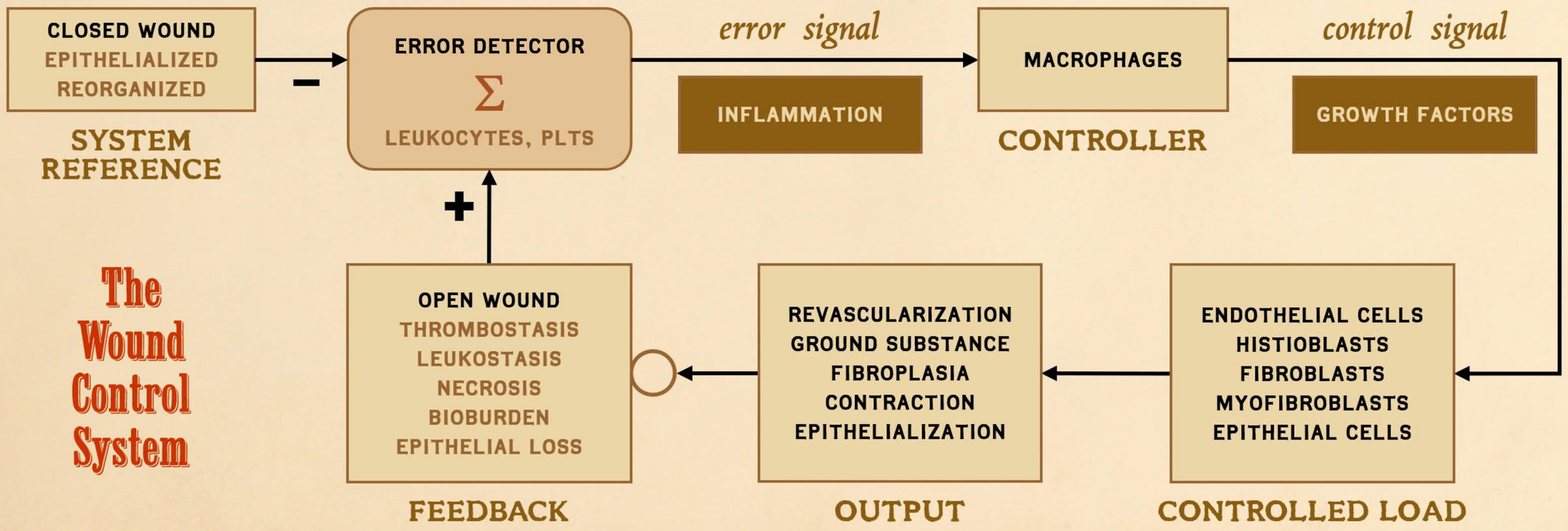

**Promoters & inhibitors, feedback and control, ensure that physiological systems stay within allowable bounds. Otherwise, the subsystem or the entire host arrests, incompatible with life.**

**UNDERSTANDING WHY HYPERCOAGULABLE STATES OCCUR, & WHY THEY ARE COMMON.**

## Endocrine Control System

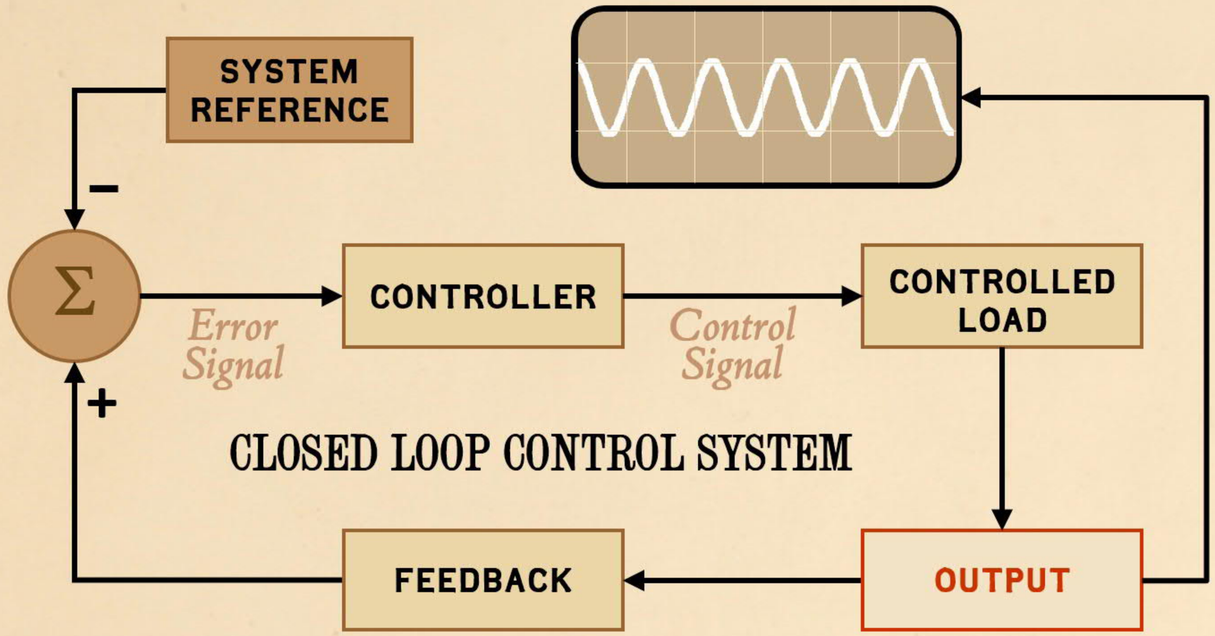



## The Wound Control System



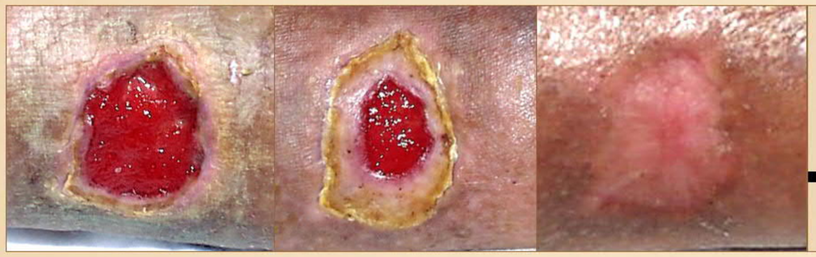
# Why do patients become hypercoagulable?

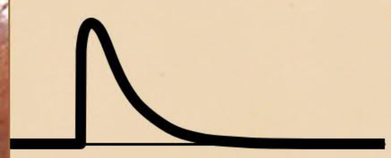
THE COAGULATION NON-LINEAR MULTI-CONTROL SYSTEM BECOMES UNBALANCED OR PERTURBED.




CLOSED LOOP CONTROL SYSTEM

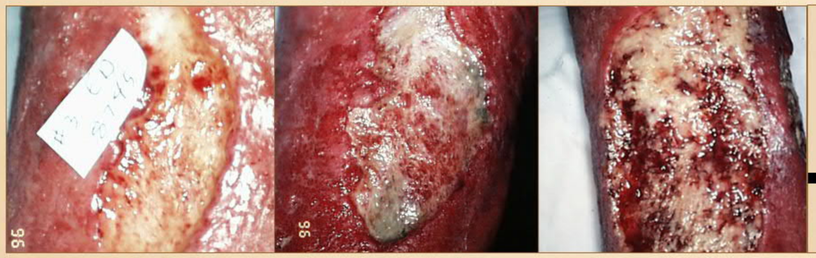
*The wound control system has three major dynamical attractors.*





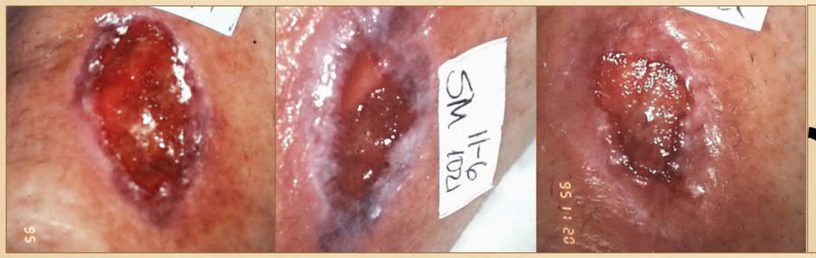
*a. one-shot*

the healthy wound
- healing –
closing
convergent



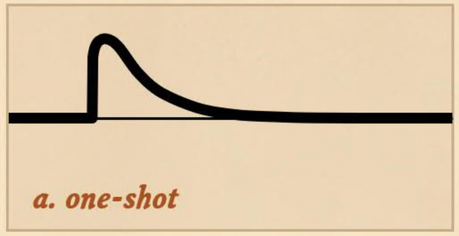
*b. saturation-extinction*

the sick wound
- ulcerating -
enlarging
divergent



*g. chaos*

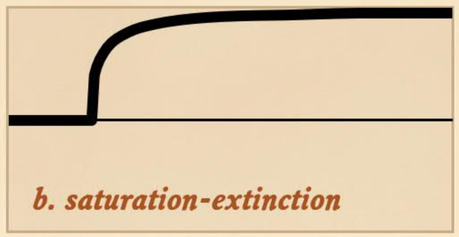
the impaired wound
- stagnant –
orbiting
chaotic



*a. one-shot*

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

The response of a healthy wound to simple injury.



*b. saturation-extinction*

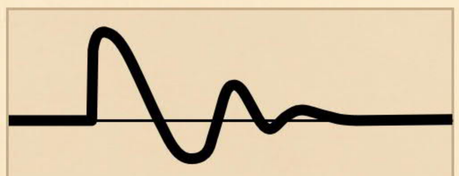
Control may fail or be over-whelmed, the system failing at its extrema.

The wound response to severe inflammation or active disease.

*c. amplification-attenuation*

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

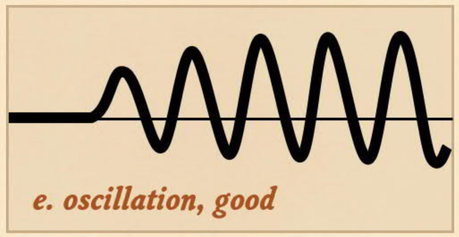
e.g. Pyogenic granuloma or keloid.



*d. damped sine*

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

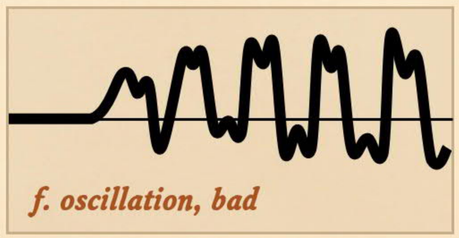
Seen in various micro-scale physiologic systems.



*e. oscillation, good*

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

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



*f. oscillation, bad*

Unintended, exaggerated, and multi-harmonic oscillations are the sum of multiple dynamics or else the bane of good control.

e.g., Parkinson or cerebellar tremor.

*g. chaos*

Moment-to-moment variations in multi-control systems can seem erratic, non-harmonic, non-analytical – aka "Chaos".

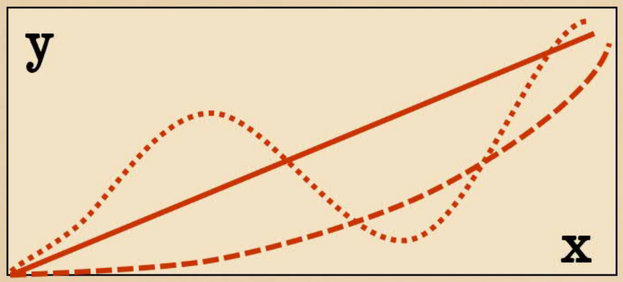
Most chronic wounds.
Unbalanced coagulation species.

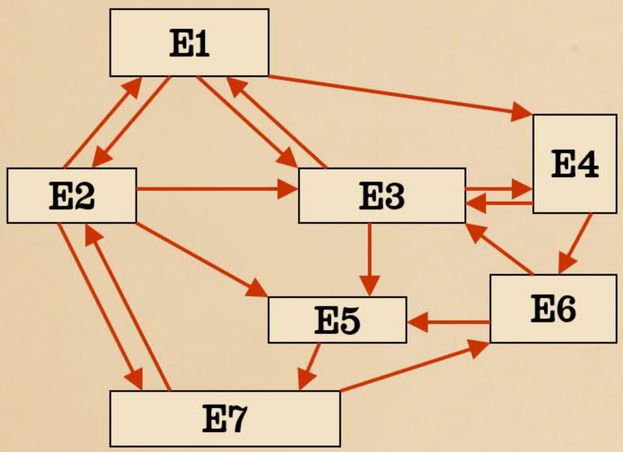
# NON-LINEAR SYSTEMS

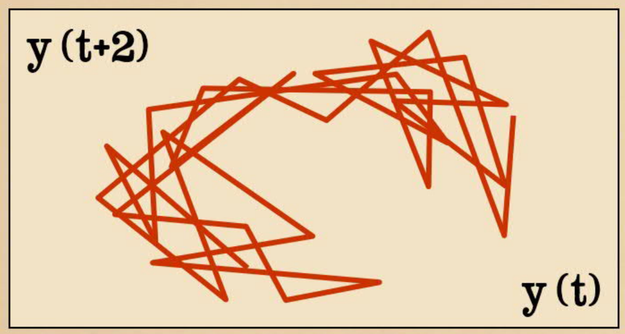
## Non-Linear Dynamics, Complexity, & Chaotic Attractors

**Non-linear & chaotic systems can have stable attractors . . .**

The system tends to "orbit", to dwell or return there.
These basins of attraction are low energy wells
that are hard to break free from.




Chaos is the behavior of non-linear and complex or multi-control dynamical systems.

Chaotic systems tend to "orbit" in attractors, basins of dynamical stability.

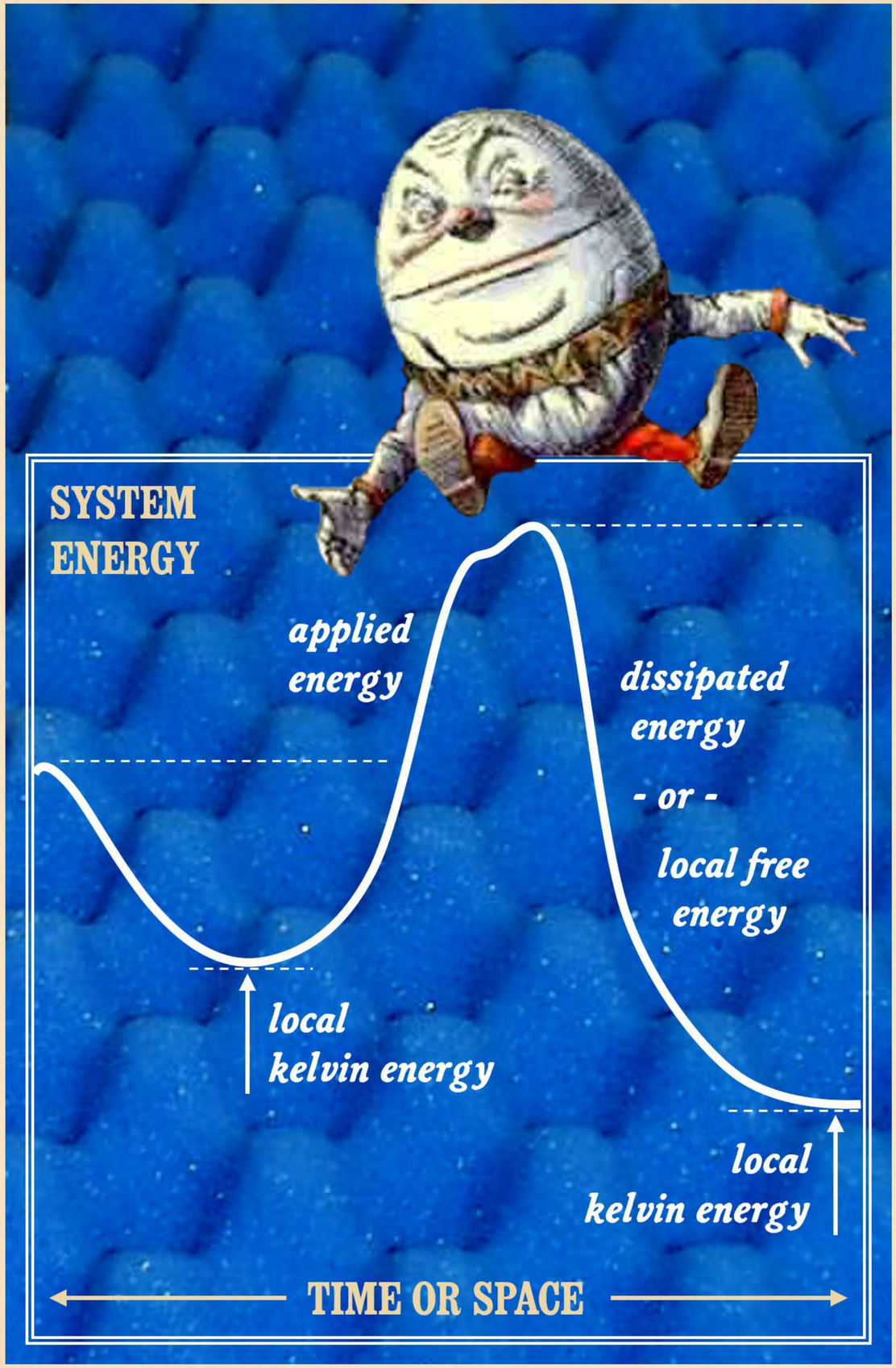
Well controlled systems can absorb or control perturbations, while untuned systems can fail.

In chaotic systems, a shift in the attractor or basin can result in undesirable outputs.

Chaotic systems are very sensitive to small perturbations or deltas causing big shifts in output.

In biological systems, a chaotic attractor might be clinically adverse, but dynamically stable and hard to alter.

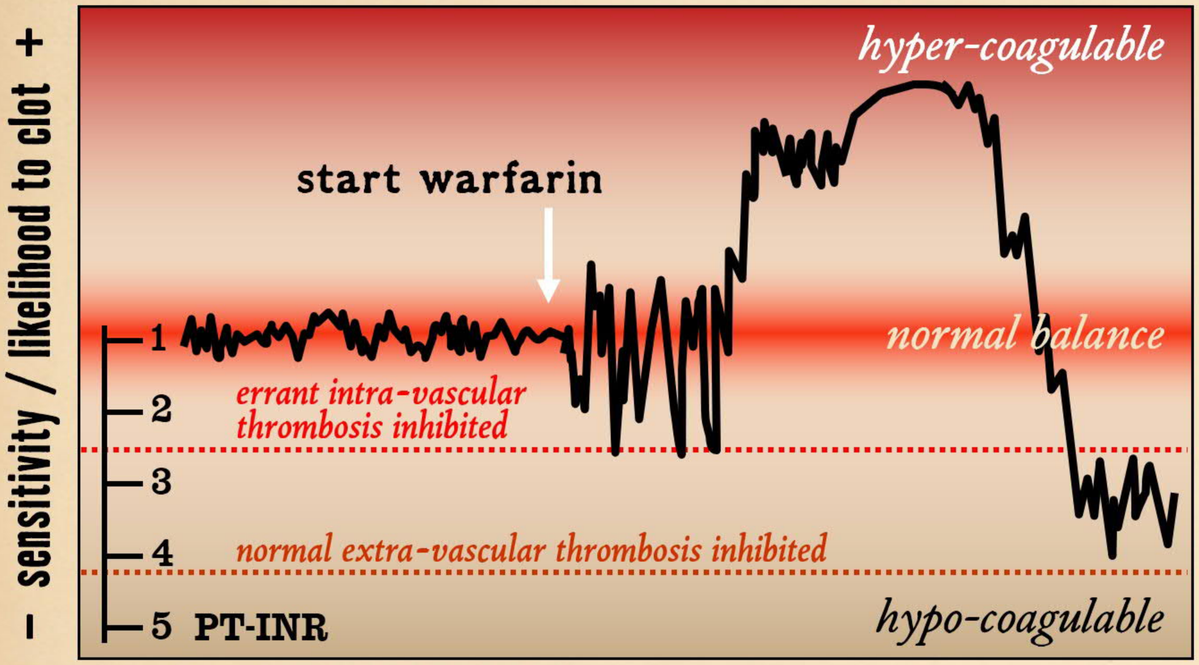
**Hypercoagulability is a Dynamical Disease.**



# Coagulation is a Complex Chaotic Non-Linear System

This has explicit implications for its physical behavior & response to variation.

This has explicit implications for pathophysiology & clinical morbidity & care.




CHAOTIC DYNAMICS IN THE COAGULATION SYSTEM

### Coagulation dynamics can become untuned and erratic.

Response to pathological stresses can be exaggerated.
Thrombosis trigger threshold can become more sensitive.
The system can "lock in" and dwell in undesirable attractors.
Bias favors thrombosis and clinical sequelae, e.g. wound pathergy.

### Hypercoagulable patients are not always coagulopathic.

Even gene mutation patients can dwell in states of normal clotting.
Laboratory profiles can look normal during quiet clinical states.
But, pro-thrombotic stresses are prone to snap to "lock in".

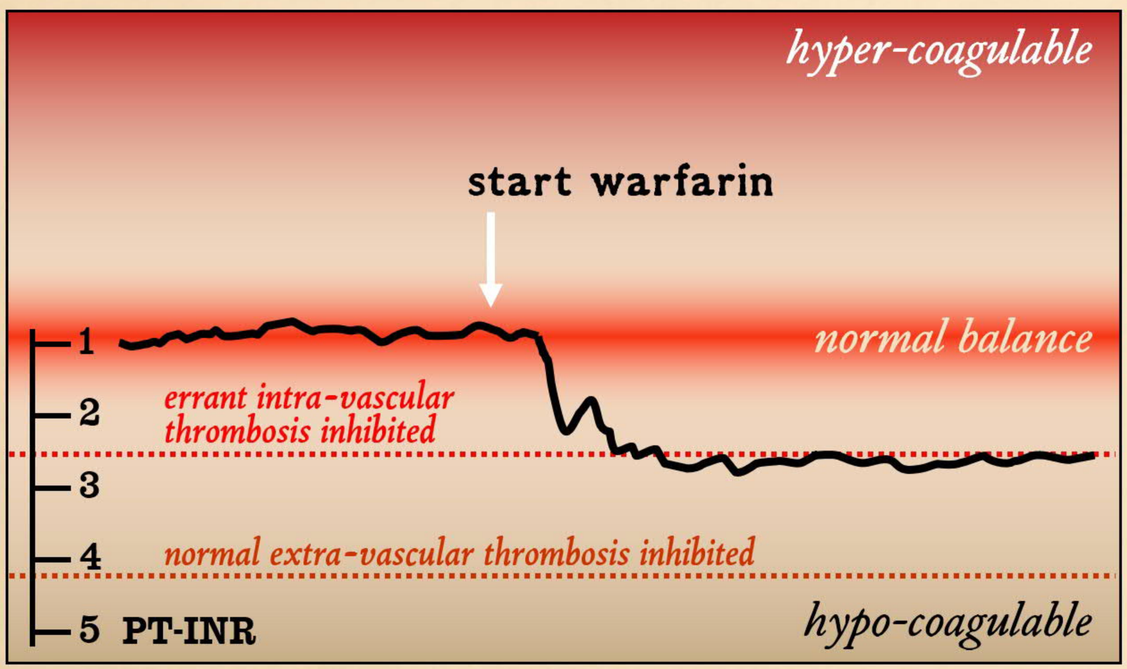
### Treatment targets and responses vary from normal blood.

Responses to Rx can be blunted, exaggerated, contrary, unpredictable.
Deliberate adjustments in Rx must be made compared to normal.

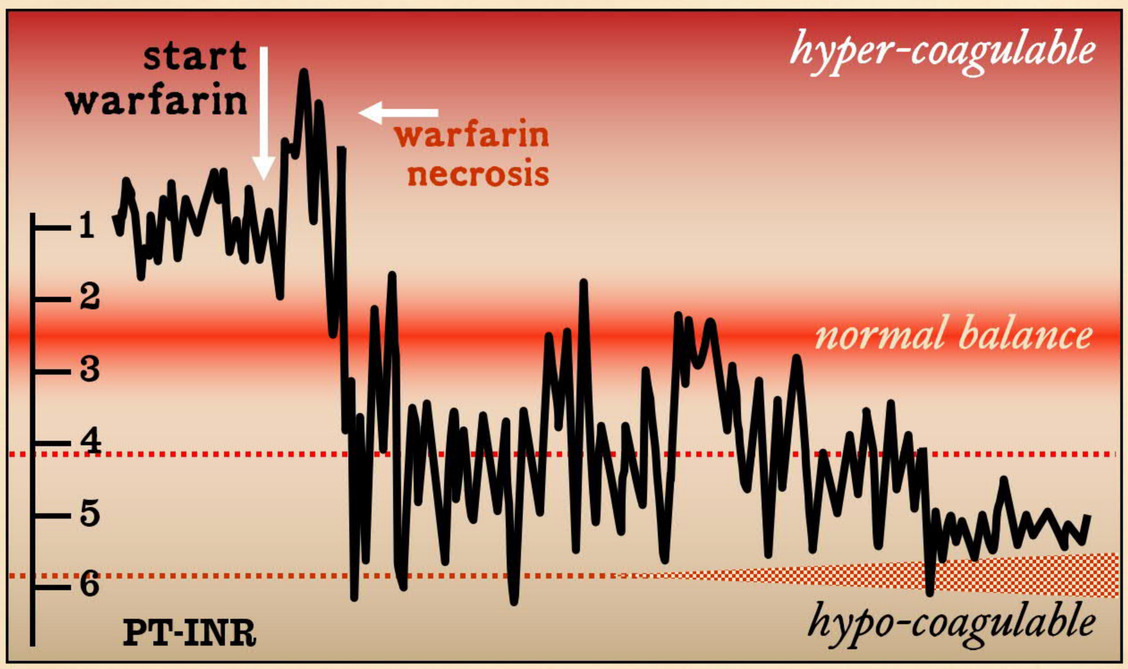
E.g. warfarin PT-INR must be high to restore blood to normal.
But, warfarin Rx can be highly erratic, unstable, unsettled.
Heparin pre-Rx to avoid pathergy (warfarin necrosis).

### As a complex non-linear multi-control system, chaos rules.

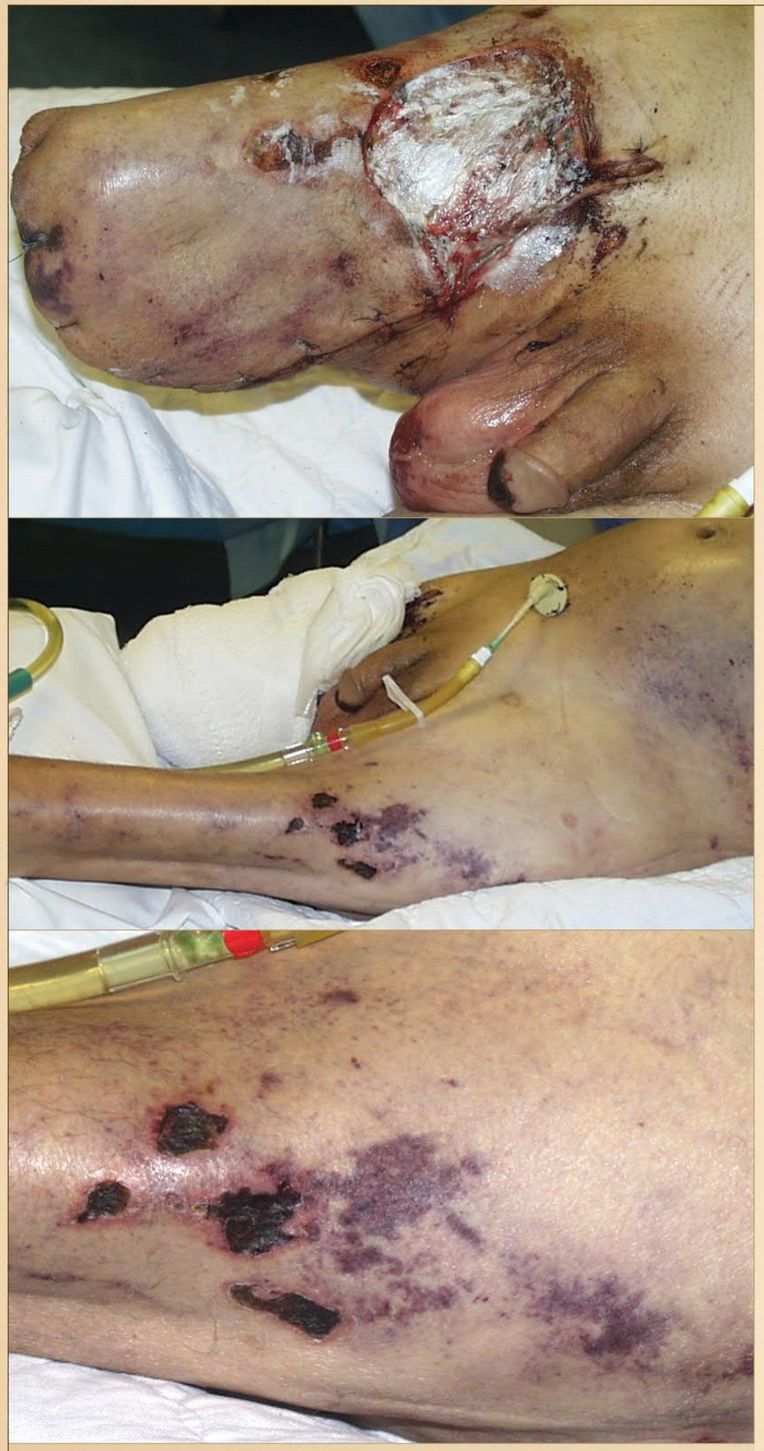
Thus, prepare for erratic and unpredictable responses to stress or Rx.




NORMAL PATIENTS




HYPERCOAGULABLE PATIENTS



**58 M** **Warfarin induced necrosis**

Coronary angioplasty.
Skin infarcts soon after starting warfarin.
No large vessel thrombi (e.g. in amputated femoral).
Lab: APC resistance high (probable factor V Leiden).

# DO NOT DO
# too much
# too soon
# too often.

*Separate debridement and wound control from repair and reconstruction.*

*Of paramount importance to good results is patience, prudence, and staged surgery.*

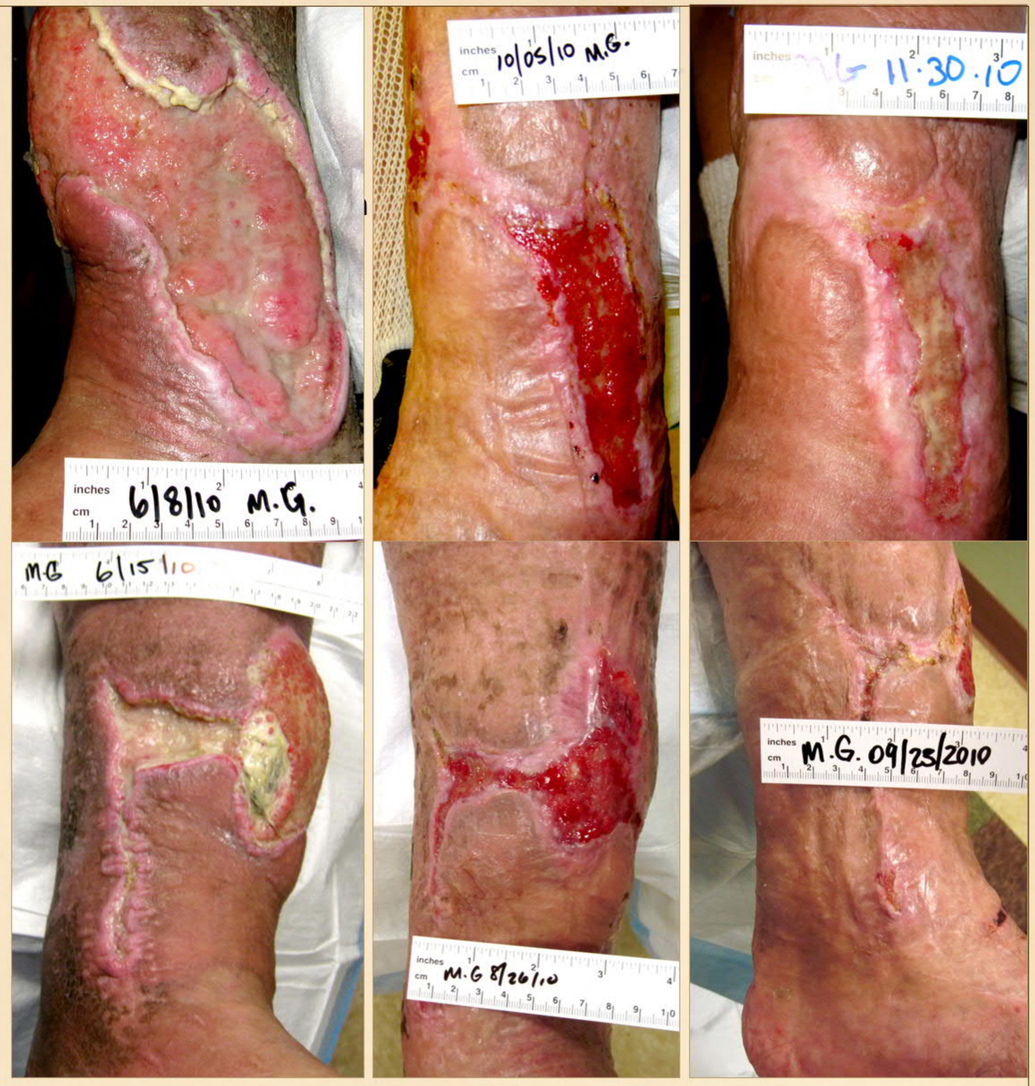
*Understand and respect biology of injury, inflammation, and wound healing.*

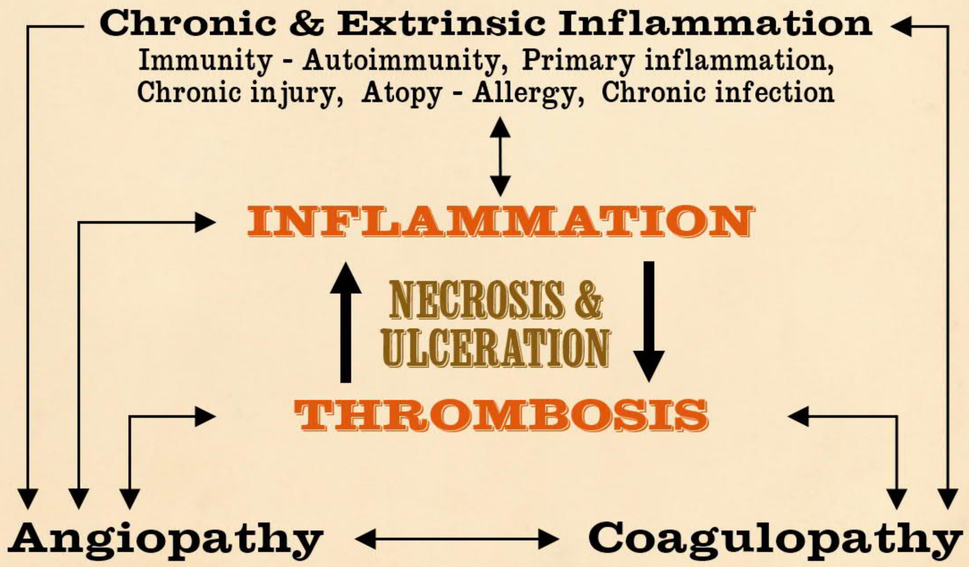
## Pathergy is Prone in Conditions of Ischemia & Inflammation

This includes macro-vascular disease, micro-occlusive & hypercoagulable, and immune disorders.

**These are conditions that mandate NOT doing too much, too soon, too often.**

**Stand down, go slow, let nature and biology recover, live to fight another day.**



# WHAT HAVE WE BEEN MISSING?

THE

SEATS and CAUSES

OF

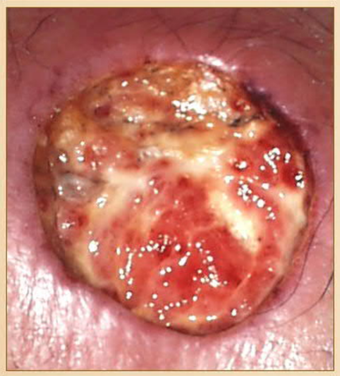
DISEASES

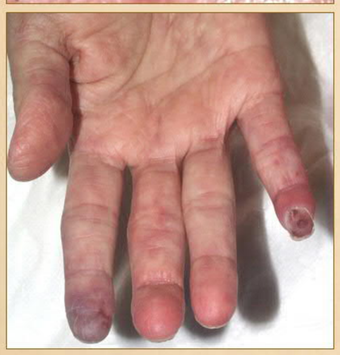
INVESTIGATED BY ANATOMY.

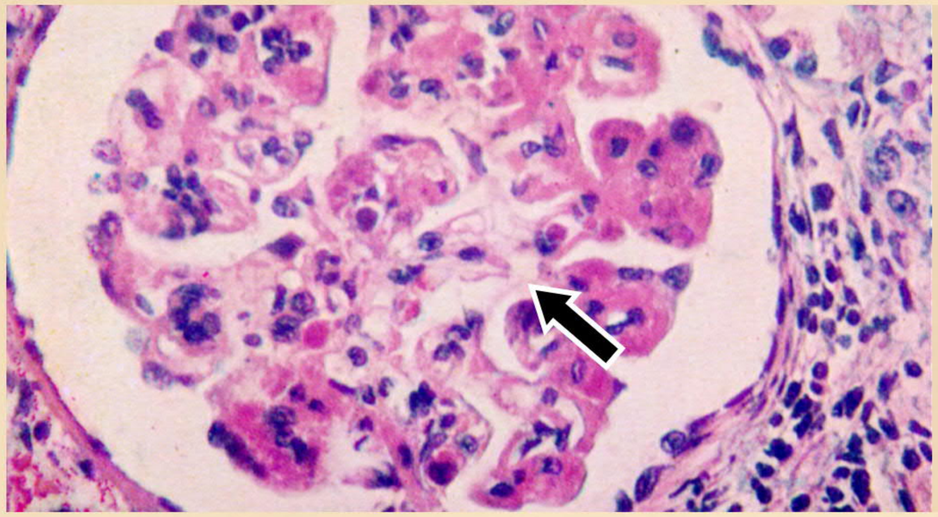
BOOK the SECOND.

Of DISEASES of the THORAX.

Zz 2





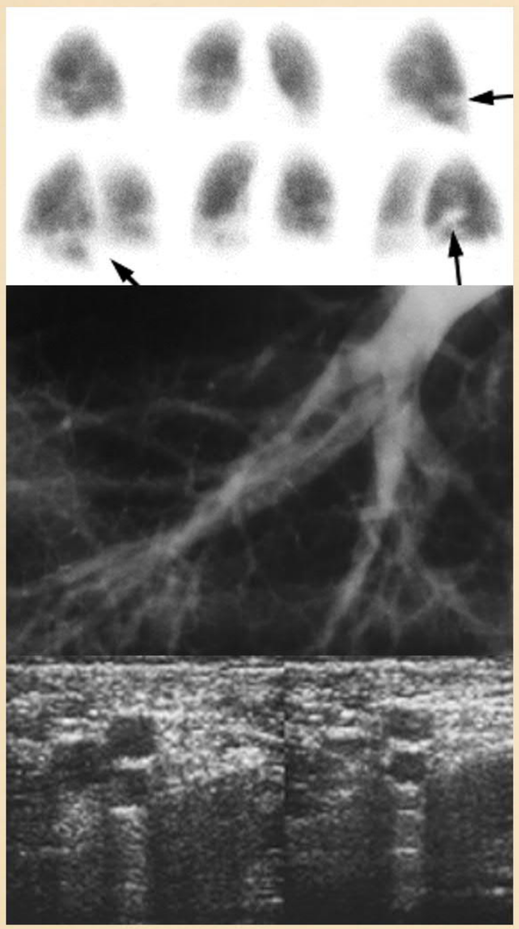


*lupus glomerulonephritis*
*focal thrombotic glomerulonephritis*
*rapidly progressive glomerulonephritis*
*glomerulonephritis of chronic liver disease*

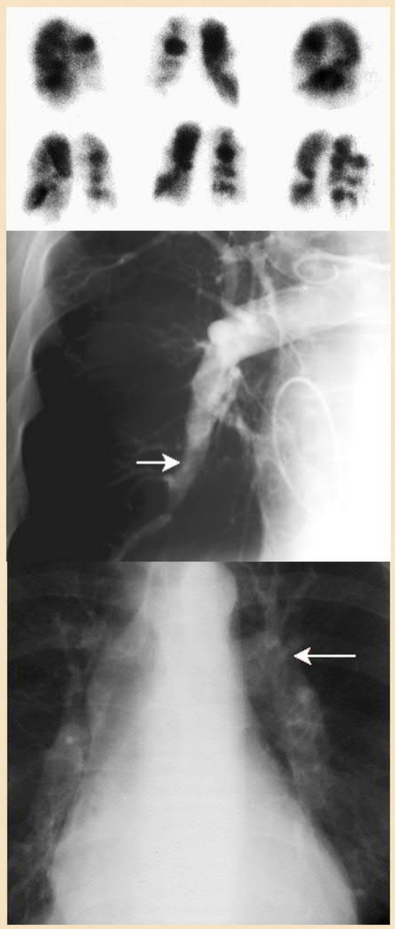
*fibrin thrombi*

**RETHINKING**
the cause, diagnosis, & treatment of classical syndromes and clinical disorders.

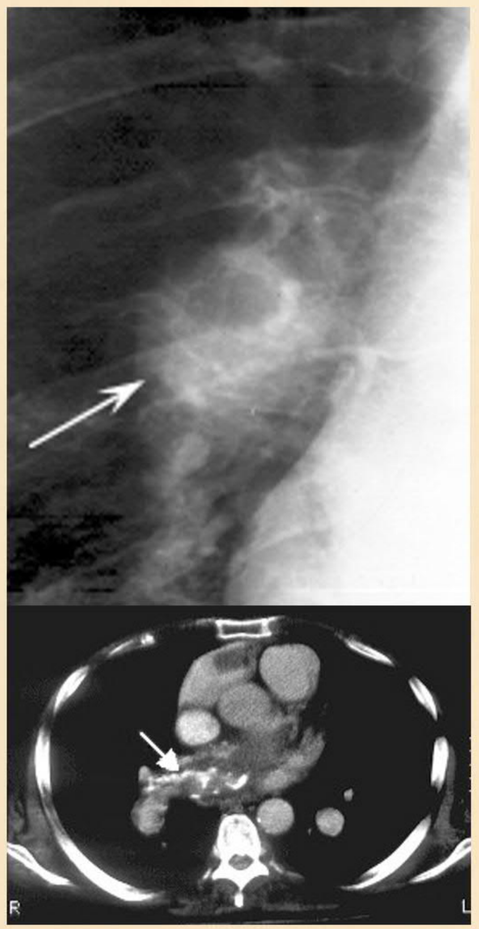
**PATHOGENESIS**
**RECOGNITION**
**APPROACH**



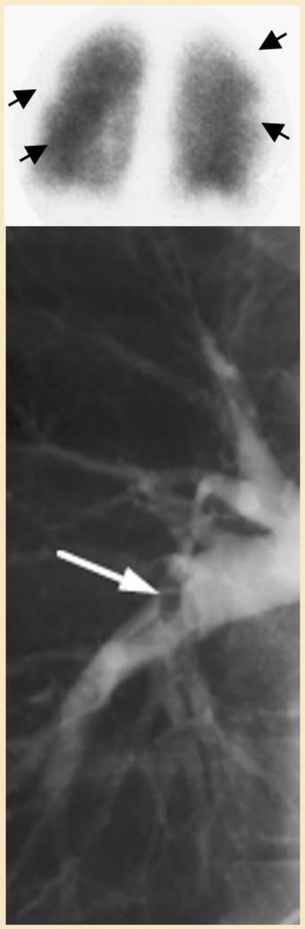
*34 f, healthy*
*subacute respiratory symptoms*
*multifocal pulmonary flow voids*
*pulmonary artery thrombus*
*clean iliofemoral veins*



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



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



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

***PPT***
*primary pulmonary thrombosis*

***ISPAT***
*in situ pulmonary artery thrombosis*

***CTEPH***
*chronic thrombo-embolic pulmonary hypertension*

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

DE HIRUDINE. LIB. IV. 431

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

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

CAPVT XVIII.

DE HIRVDINE, SIVE SANGVISVGA.

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

Guillaume van den Bossche
*Historia Medica* 1639

## Hypercoagulability

A modern discovery and concept.

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

## Positive Diagnosis

They can be diagnosed on specific criteria.

**Hypercoagulable disorders & ulcers are NOT diagnoses of exclusion.**

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

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

**Recognize the tetrad-pentad syndrome.**

## Hypercoagulable Syndrome

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

## Pathophysiology & Triggers

Complex multi-control system, NLD.

Affected pt's are not always coagulopathic.

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

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

## Wounds, Trauma, & Surgery

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

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

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

## Anticoagulation

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

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

Treatment parameters are different than "thinning" normal blood.

Anticoag. Rx restores normal wound healing.

## Comprehensive Treatment

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

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

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

## Managing Surgery

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

**Run anticoagulants during surgery.**

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

Marc E. Gottlieb, MD, FACS
Phoenix, AZ


September 20, 2018 (original presentation)
September 23, 2018 (update, Revision 01-b)

# ARIMEDICA

www.arimedica.com

Marc E. Gottlieb, MD, FACS
Phoenix, AZ

# XENO