PRETHROMBOTIC AND MICROTHROMBOTIC DISORDERS

HYPERCOAGULABILITY

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Hypercoagulability: Prethrombotic and Microthrombotic Disorders

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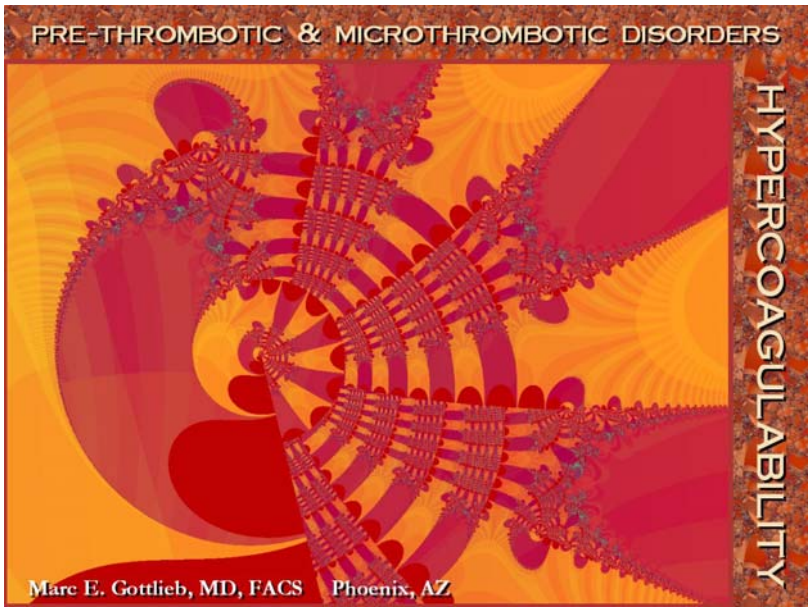
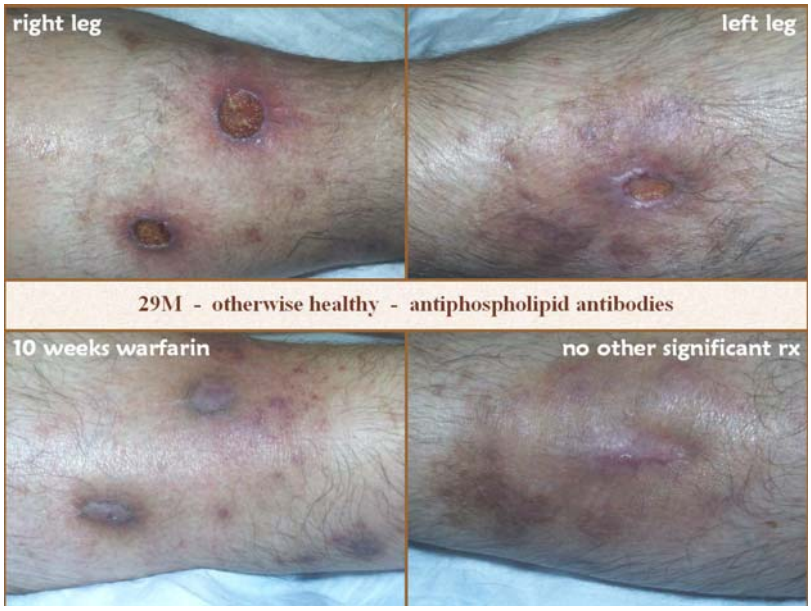


SLIDE 1

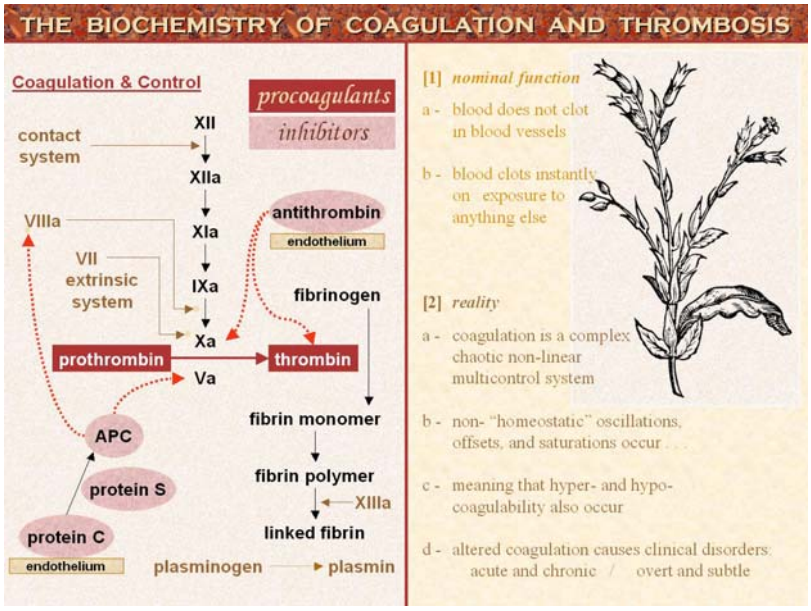
A presentation concerning hypercoagulable and microthrombotic disorders, with the focus on the intrinsic alterations of the coagulation system itself, i.e. the "prethrombotic disorders".

This is a talk about general hypercoagulability. It is not a wound talk, but since my own practice concerns wounds and soft tissue pathology, the patient examples are largely wound patients. The lessons learned here can be readily extrapolated to disorders of other systems.



SLIDE 2

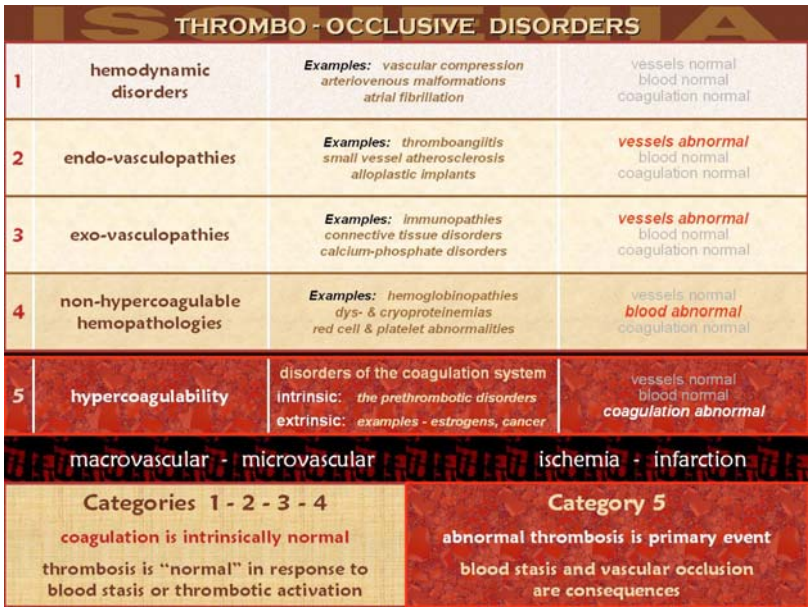
To illustrate the significance of the prethrombotic hypercoagulable disorders, this example is a 29 year old man, otherwise completely healthy, who has had leg ulcers for many years. They intermittently heal, and the discolored areas on his legs attest to old ulcers. The current ulcers on both legs have been present two years. He has had otherwise thorough care in a wound clinic for one year, without any improvement. The patient's clinical profile and non-response to other therapy points towards hypercoagulability. Workup confirms high anticardiolipins. After two years of no response to any therapy, he was started on warfarin. With absolutely no other changes in care other than the warfarin, what would not heal over two years is healed after just 10 weeks of warfarin therapy.

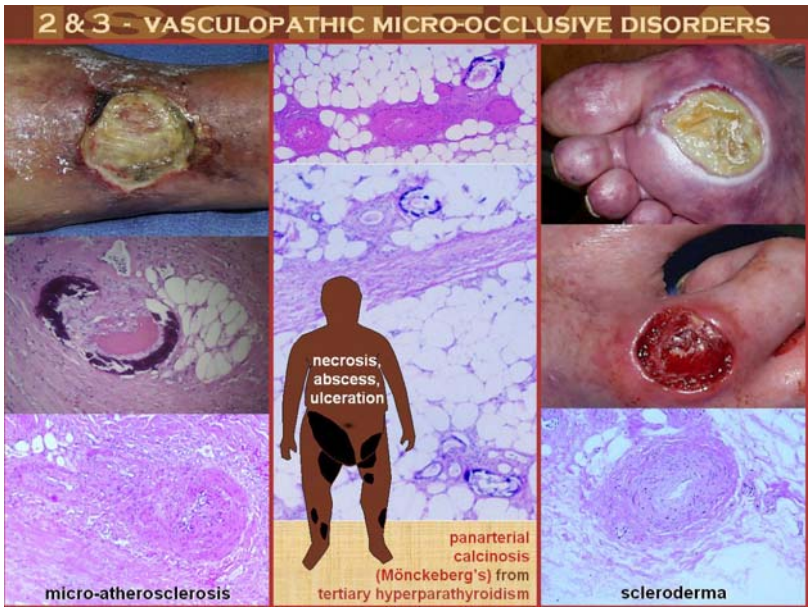


SLIDE 3

Coagulation is a complex system of a dozen main-sequence proteins, and dozens of cofactors and modulators. The nominal function of the system is to remain passive when blood is where it belongs in endothelial conduits, but to respond and clot instantly on exposure to anything else.

The reality is that coagulation is a complex non-linear multicontrol system. Amazing that it works so well, it is no surprise that the system will be prone to non-homeostatic variances, including offsets that render the system hyper- or hypo- coagulable. The clinical consequences of these variances or failures run the gamut of acute and chronic, overt and subtle, inconsequential and lethal.





SLIDE 4

There are many causes of abnormal thrombosis and vascular occlusion, grouped here according to this scheme:

1 - Hemodynamic disorders: Blood, blood vessels, and coagulation are all normal. Blood clots as it is programmed to do in response to abnormal hemodynamic conditions.

2, 3 - Endo- (intrinsic) and exo- (extrinsic) vasculopathies: Blood and coagulation are both intrinsically normal. Clotting is activated by abnormal blood vessels.

4 - Non-hypercoagulable hemopathologies: Disorders of various blood components lead to conditions of stasis which trigger thrombosis. The coagulation system itself remains intrinsically normal.

In these first 4 categories, the coagulation system is normal, responding appropriately to abnormal conditions created not by trauma and bleeding, but by other undesirable pathologies.

5 - The hypercoagulable disorders lead to abnormal, mis-programmed thrombosis. These disorders may be extrinsic, triggered by other abnormalities such as estrogens, pregnancy, cancer, inflammatory disorders, and others which affect the coagulation system. These disorders may also be intrinsic alterations of the coagulation system itself.

In the hypercoagulable disorders, abnormal thrombosis is the primary event. This is turn leads to blood stasis and vascular occlusion, the reverse of what happens in the other categories.

The consequences of thrombotic occlusion are the same regardless of mechanism. The process may be sudden or progressive, involving large or small vessels, but it all leads to ischemia of one degree or another, with infarction and necrosis being the extreme outcomes.

SLIDE 5

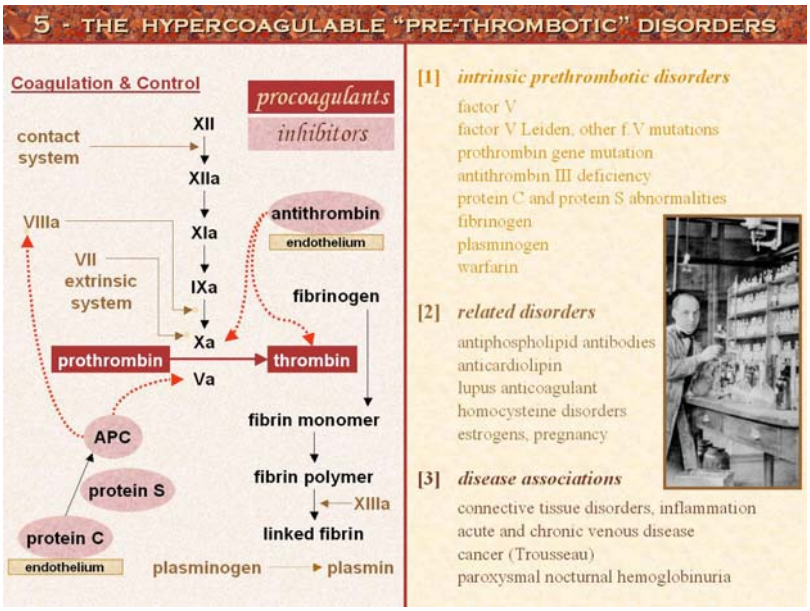
Illustrations of the non-hypercoagulable microthrombotic disorders. Slide 5 shows micro-vasculopathic disorders. The first patient has microvessel as well as large vessel atherosclerosis, leading to severe, refractory, essentially untreatable ulcers. The second panel shows one of the complications of severe hyperparathyroidism: medial arteriosclerosis involving all small arteries. The consequence is tissue deoxygenation, multiple infarctions, and delayed healing. The third panel shows patients with scleroderma and the vascular pathology that can accompany this disease.

The main lesson of this slide is that histopathology can be very useful in the evaluation of these patients and those with any soft tissue pathology. Biopsy and microscopic evaluation not only establish uncertain diagnoses, but they can be a good guide to prognosis and treatment.

SLIDE 6

Many of the hemopathologies cause microvascular occlusion which in turn leads to focal thrombosis, ischemia, and infarction. When infarction occurs in the skin, the clinical result is an ulcer. Sickle disease is a paradigm of this pathophysiology, but all of the listed disorders can have similar complications.

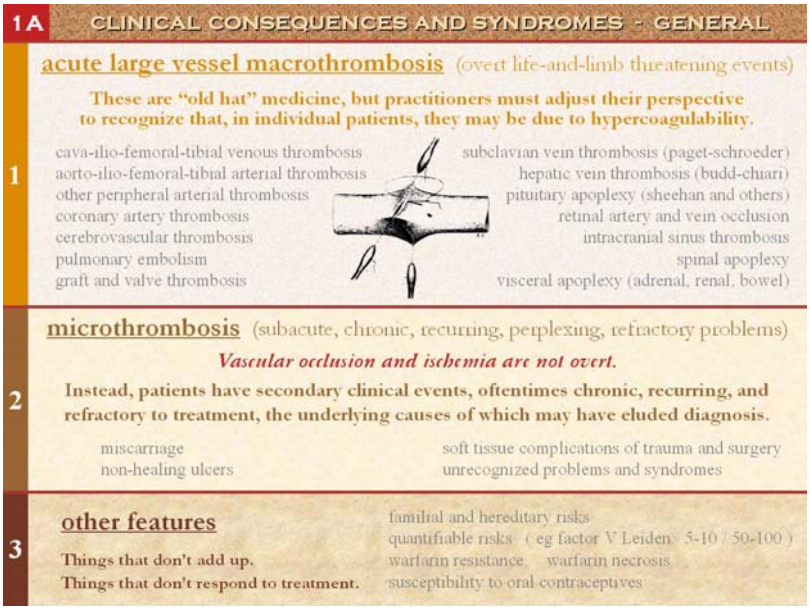
To the extent that pathological activity continues, ischemia, infarction, and related symptoms persist, and resolution of these sequelae can be difficult. Skin ulcers related to these disorders are notoriously difficult to resolve, but recent technological modalities of care have improved the prospects substantially.



SLIDE 7

Hypercoagulability includes variances of intrinsic coagulation factors and other disorders related to the coagulation system. Presumably, dozens of "disorders" are yet to be discovered among the coagulation factors. The thrombotic factors listed are simply the ones that have a clinical lab test that can be ordered (probably they are the more prevalent disorders which is why they have been discovered and lab assays developed). Warfarin is included because of its direct effect on coagulation factors and the thrombosis and infarction that it can cause (due to transient imbalances in affected factors as warfarin is started). Other factors, some in association with connective tissue disorders, also induce or trigger coagulation imbalances.

Aside from intrinsic imbalances in the chemistry of thrombosis, there are pertinent associations with other diseases. A cancer association is long recognized, and associations with immunopathies are common. Other thrombotic disorders, such as PNH, have some kind of interrelationship with the thrombotic systems. "Venous disease" and ulcers may be a consequence of repeated thrombosis and venous hypertension, but the thrombosis may be due to hypercoagulability, and the ulcers may be due to the hypercoagulability alone.

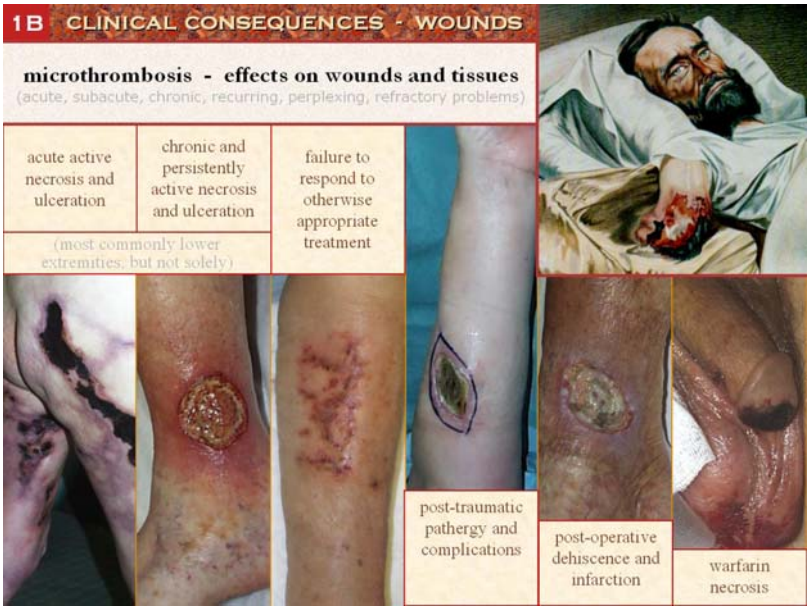


SLIDE 8

Hypercoagulability leads to large and small vessel thrombosis. Large vessel occlusion is often acute, overt, and immediately serious. Vascular occlusive events are well recognized and understood, but practitioners need to readjust their perspective on these problems. They need to recognize that when they occur, a hypercoagulable disorder may be responsible, and that there may be other underlying triggers or a risk of recurrent episodes. Nearly all of the gross conditions listed have now been reported in association with the prethrombotic disorders.

When microthrombosis occurs, the problem is often subtle or arcane. Patients have secondary manifestations, such as leg ulcers or miscarriage, which are chronic or recurring and refractory to usual treatments. Any effort to find customary underlying diagnoses fails.

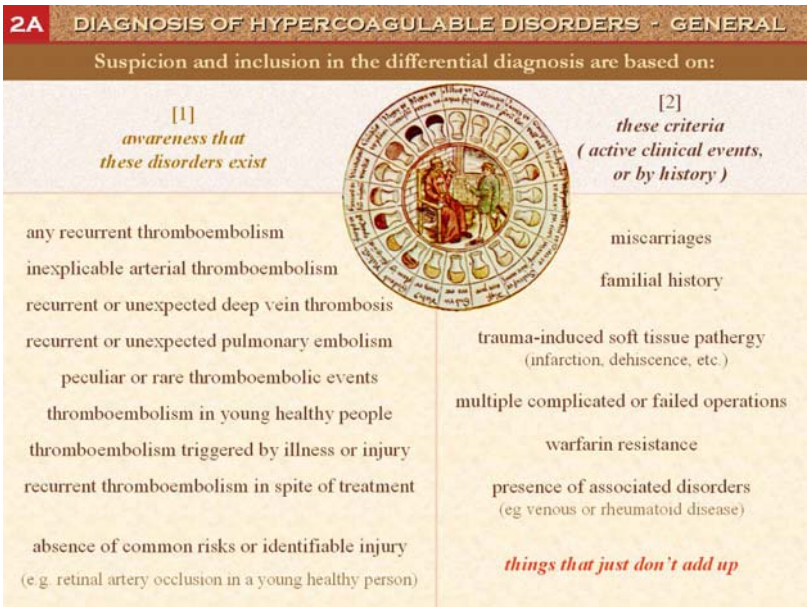
Other issues to consider include the familiality of some of these disorders, so family history is important. These disorders increase risk of thrombosis with other thrombogenic agents. Some of the risks are quantifiable: V-Leiden heterozygous is estimated to have a 5-10 fold risk of thrombosis over the general population, 50-100 fold for homozygotes.



SLIDE 9

When hypercoagulable microthrombosis affects skin and soft tissues, there are certain predictable and identifiable patterns of pathology which emerge. These effects can be acute, chronic, recurring. Until a proper diagnosis is made, the problems will be considered perplexing and refractory to care.

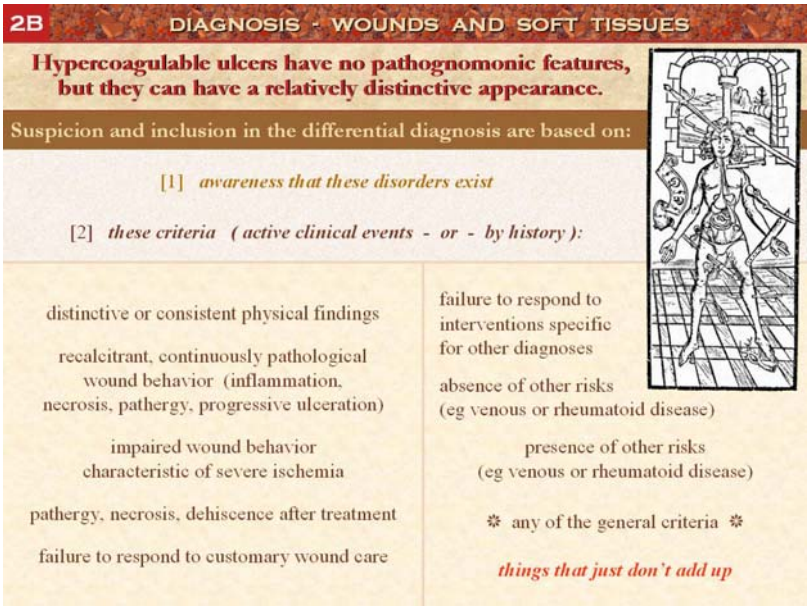
Necrosis and ulceration may be acute and active, subacute and subtle, or persistent and chronic, with failed wound healing, even when active necrosis has subsided. Otherwise appropriate treatment will fail or be only partially effective. Pathergy is the notion that injury causes unexpected or disproportionate necrosis and complications within the soft tissues. Several disorders can cause this (any severe ischemia, pyoderma gangrenosum, uncontrolled immunopathies), and it is also a common effect of the hypercoagulable disorders. When it occurs after surgery, the result is dehiscence and related problems. Warfarin necrosis, a long recognized adverse but transient effect of this occurs as warfarin creates temporary imbalances in the level of vitamin K clotting factors. It seems that this is more likely to occur in those patients already imbalanced due to prethrombotic disorders.



SLIDE 10

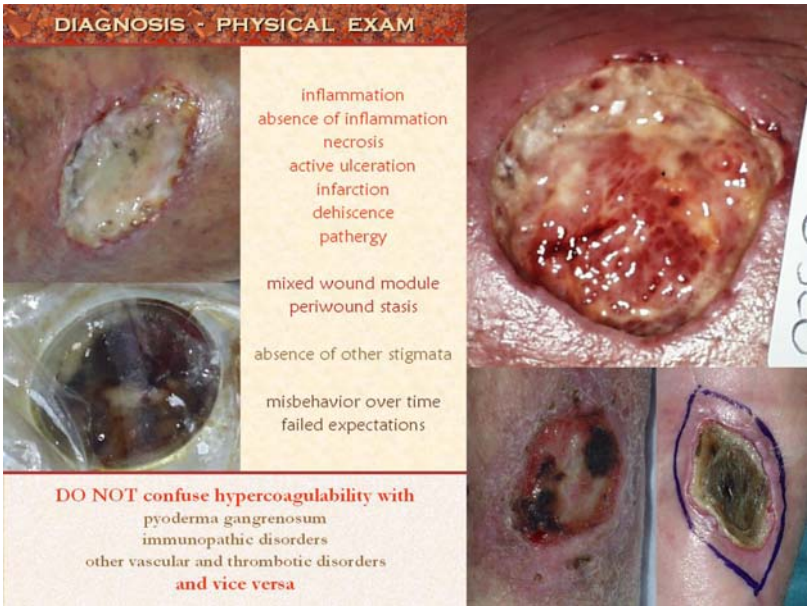
How does one recognize and diagnose these disorders? Remember, the patient presents with some overt clinical syndrome. What leads you to suspect that hypercoagulability is the culprit? The exact diagnosis will depend on laboratory confirmation, but inclusion of these disorders in the differential diagnosis is based on some distinctive features. History of the present illness, the past medical history, and the family history ALL give crucial insights.

Any history or occurrence of recurrent, uncommon, or inexplicable thrombosis should be suspect. Thrombosis and embolism in otherwise young or healthy people should be suspect. Thrombosis in spite of treatment, and resistance to anticoagulants should be suspect. Thrombosis associated with immunopathic disorders should be suspect. A history of post-traumatic wound and tissue complications, multiple failed operations, a history of miscarriage, and a family history of any of these problems should be suspect.



SLIDE 11

Wounds and necrosis due to hypercoagulable disorders do not have any pathognomonic features, but they do have characteristic appearances and behaviors. Most of the features of hypercoagulable wounds which lead to their recognition and diagnosis are those features described on Slide 9. Key concepts are the recalcitrant continuously pathological behavior of the wounds, progressive necrosis and ulceration, impaired wound healing, and failure to respond to other usual care. Discrimination of hypercoagulable from other common ulcers is easy to do, although hypercoagulable and immunopathic ulcers are very similar and require explicit discrimination based on laboratory evaluation.

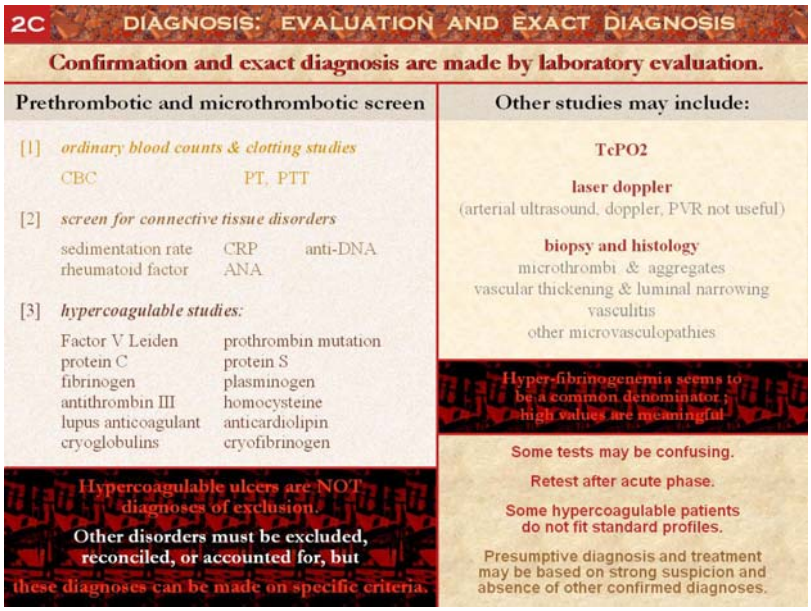


SLIDE 12

Inclusion of hypercoagulability in a differential diagnosis is based on history and physical examination. What are the physical exam features that are relevant? With regard to wounds and soft tissues, the physical findings all reflect the effects of vascular obstruction and ischemia, as described on Slide 9. This slide demonstrates characteristic appearances.

Any ulcer can be inflamed due to injury or lack of adequate care. However, many hypercoagulable ulcers are devoid of gross inflammation (there are no specific triggers to inflammation after this kind of non-platelet thrombosis). This is a key feature which can discriminate hypercoagulable from immunopathic disorders.

Pyoderma, immunopathy, and various forms of vascular insufficiency can lead to similar ulcers, events, and physical features. These various diagnoses can be and are confused by the unwary. The proper treatment for all of these problems is very different.

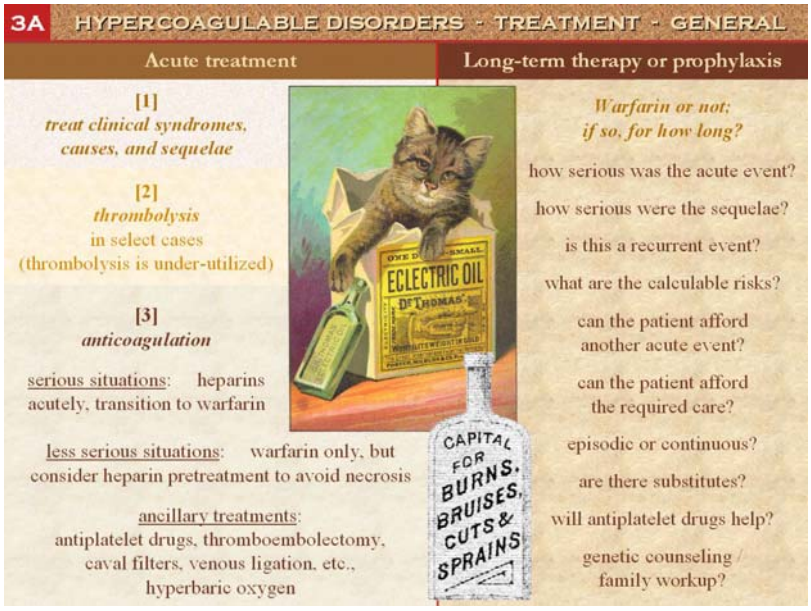


SLIDE 13

To confirm or disprove hypercoagulability, laboratory tests are done. These tests do not actually prove hypercoagulability. They simply document that there is an objective identifiable factor in the blood that is known to cause or be associated with hypercoagulability. Combined with the active clinical events and the history and exam, a positive objective laboratory test simply confirms what was at or near the top of the differential diagnosis.

Measurements of coagulation factors are essential, but the laboratory also provides other diagnostic support. TcPO2s are very helpful to confirm microvascular occlusion, especially in people with good pulses whose macrocirculation is unimpeded. Laser dopplers, while not commonly available, provide similar information. Large vessel vascular studies are generally useless for assessing microthrombosis. Biopsies, often as a wound debridement, can provide essential confirmation of microthrombosis or other useful diagnostic information.

If some positive studies are suspected of being “acute phase reactants”, retest when acute events and inflammation subside. Negative tests do not entirely rule out the diagnosis – clinical profile is essential.



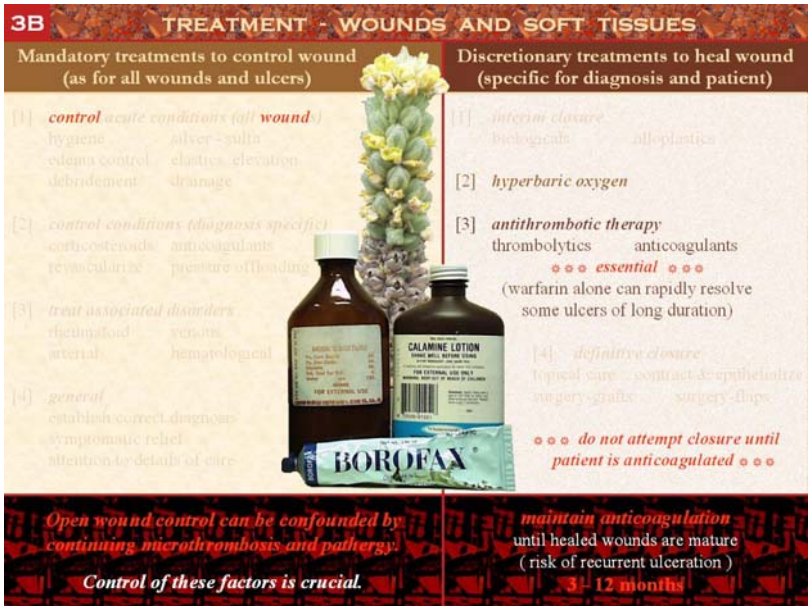
SLIDE 14

Once a diagnosis of hypercoagulability is made, treatment must be decided. Such decisions will be based on the type of overt clinical event and its severity, recalcitrance to care, and risk of recurrence.

Treating the overt problem resulting from hypercoagulability is the first order of business. Thrombolysis seems to be used infrequently in this local area (Phoenix), but it is used more commonly in some other places.

Anticoagulation is the main form of treatment. In serious situations, heparins and warfarin may both be used, warfarin only in less urgent situations. Heparin pretreatment should be considered to avoid risk of warfarin necrosis. Miscellaneous treatments must also be evaluated for each individual case. Hyperbaric oxygen is also a good option for select patients.

Once the acute problem is resolved, how long should treatment continue? There are many issues to consider in deciding the answer for each patient.

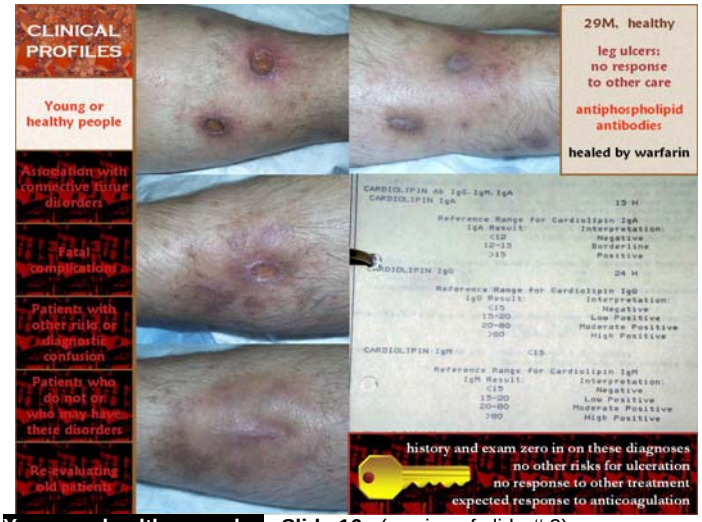


SLIDE 15

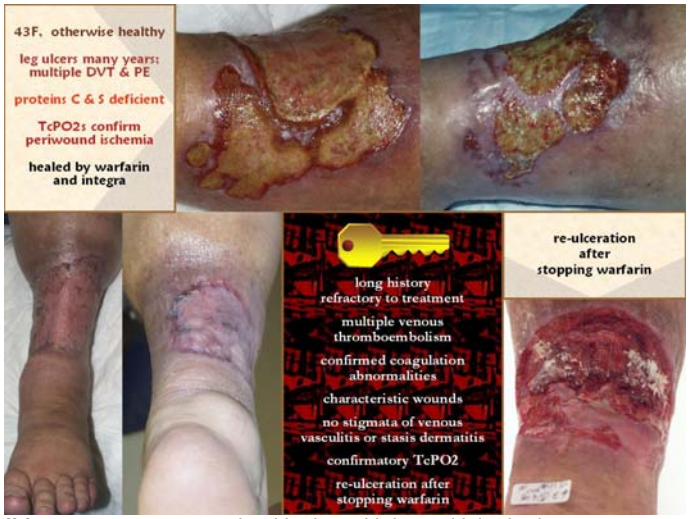
This is not meant to be discussion of wounds per se, so much of the information directly relevant to wound care can be ignored. A few principles of wound care stand out though when trying to manage hypercoagulable ulcers.

As with any wound, the first order of business is to get the wound under control: no inflammation, no sepsis, no eschar, no necrosis, no edema, no symptoms nor risk to the patient. After that, one must choose discretionary options for the definitive resolution or long term control of the ulcer. For hypercoagulable and other microthrombotic ulcers, anticoagulants are essential. Hyperbaric oxygen is a valuable adjunct. Surgery must be considered carefully, and artificial skins such as integra are valuable options. Thrombolysis has been reported for hypercoagulable wounds, but is generally unnecessary, since old microthrombi will lyse as long as new thrombosis is prevented.

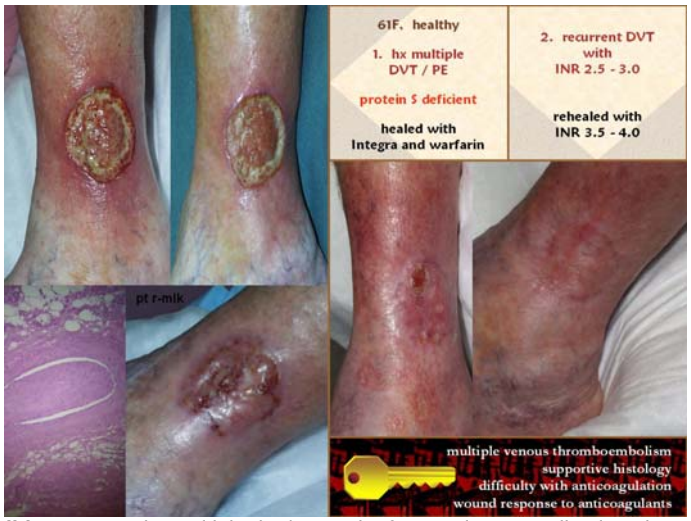
Because of the risk of pathergy, it is preferable to anticoagulate patients prior to doing any surgery. Re-ulceration is a risk in recently healed wounds, and anticoagulation should continue until the wound and scar are sufficiently matured.



Young or healthy people. **Slide 16** (reprise of slide # 2). Young healthy man with no other identifiable risks for leg ulcers. No response to any other care; complete and rapid resolution only by adding warfarin. Ulcer distribution and appearance typical of hypercoagulability.



Slide 17 Young woman, healthy but with hx multiple dvt / pe. Severe refractory leg ulcers. Confirmed hypercoagulability. Consistent TcPO2s. Wound response to increased warfarin. Warfarin-integra-hbo resolved wound. Re-ulceration of immature skin when patient ran out of warfarin.

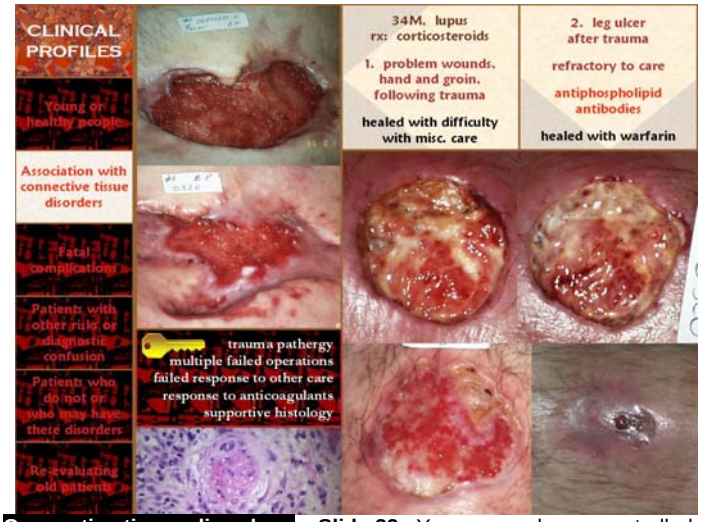


Slide 18 Long hx multiple dvt / pe and refractory long-standing leg ulcer. Confirmed Protein S abnormality. Response to up-regulated warfarin plus integra. Severe acute dvt on therapeutic warfarin. Fully resolved with further increase in pt-inr. Confirmatory histology.

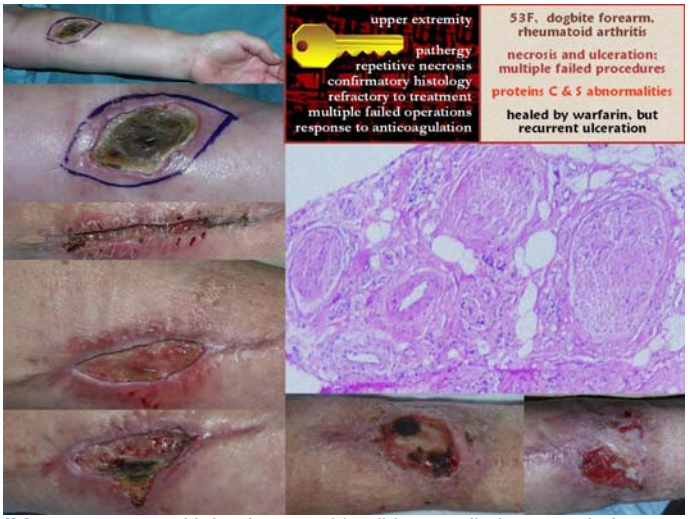
Slide 19 Non-healing ischemic type leg ulcer, but with good arterial pulses. Necrosis-dehiscence after trivial excision and closure. No wound module with basic care. Resolved with warfarin-integra. Consistent histology and gross appearance.

Slide 20 Young woman otherwise healthy. 2-year hx relentless necrosis, failed vascular procedures and amputations. Failure to recognize peculiar profile and work patient up. High homocysteine. Confirmatory TcPO2s. Proper response to warfarin-integra-hbo.

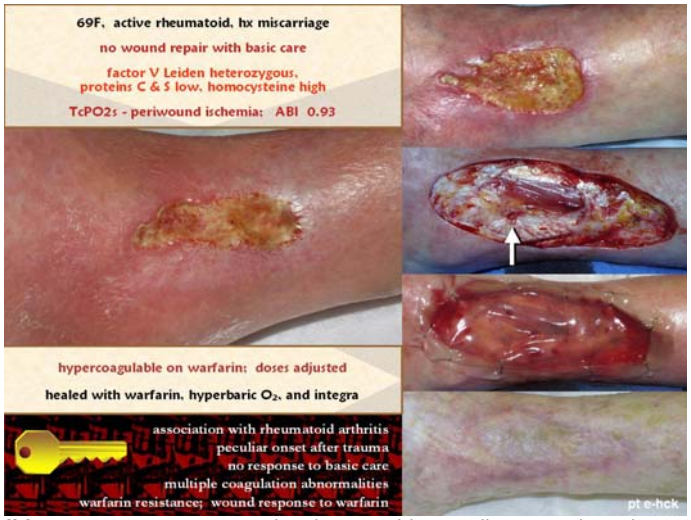
Slide 21 Young, healthy. Multiple pathergy, necrosis, failed surgery after spontaneous achilles rupture. Unexpected necrosis after minor surgery. Hx retinal artery occlusion-blindness. Abnormal tests remain positive after acute phase. Uncomplicated resolution with warfarin-integra-hbo.



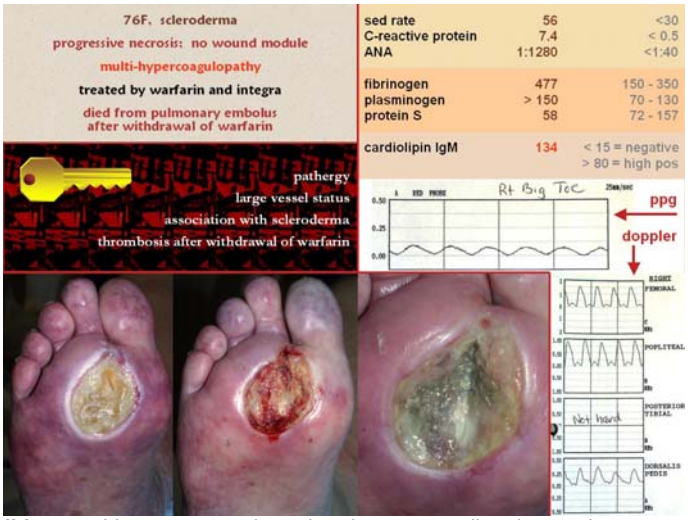
Connective tissue disorders. **Slide 22** Young man, lupus, controlled. Multiple necrosis, dehiscence, ulceration after multiple lacerations. Multiple failed surgery. No response to any care. Integra failed by itself. Anticardiolipin positive. Immediate thorough response to warfarin only.



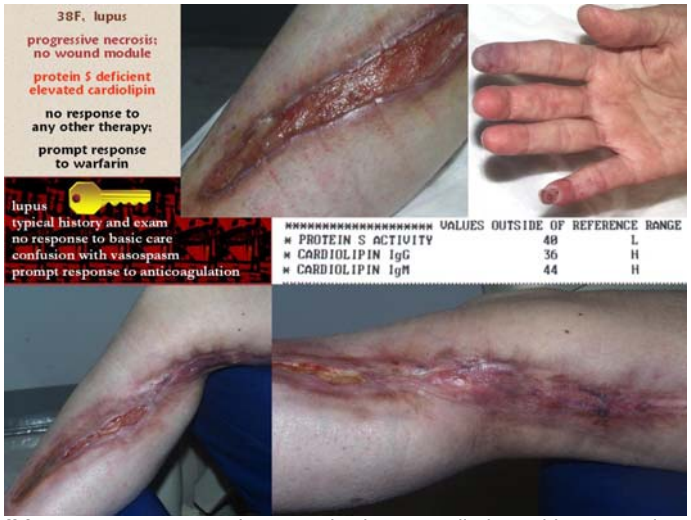
Slide 23 Woman with hx rheumatoid, mild, controlled. Necrosis forearm wound after dogbite. Multiple necrosis or dehiscence with each of many operations. Integra by itself failed. Protein C & S abnormalities. Positive histology. Healed with warfarin, but recurrence when warfarin stopped.



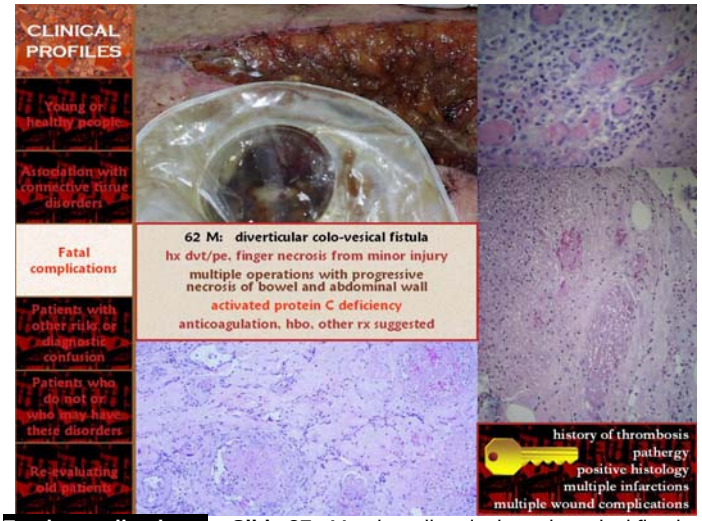
Slide 24 Woman, severe active rheumatoid. Peculiar necrosis and inflamed ankle ulcer after knee replacement. No wound module after control of inflammation. V-Leiden, other abnormalities. Hypercoagulable with nominal therapeutic pt-inr. Healed with higher warfarin and integra.



Slide 25 Elder woman, active scleroderma. Peculiar plantar ulcer. Pathergy-necrosis after debridement, despite adequate macro-circulation. Digital ischemia. Multiple coagulopathy. Good initial response to warfarin-integra. Fatal pulmonary embolus after withdrawal of anticoagulants.

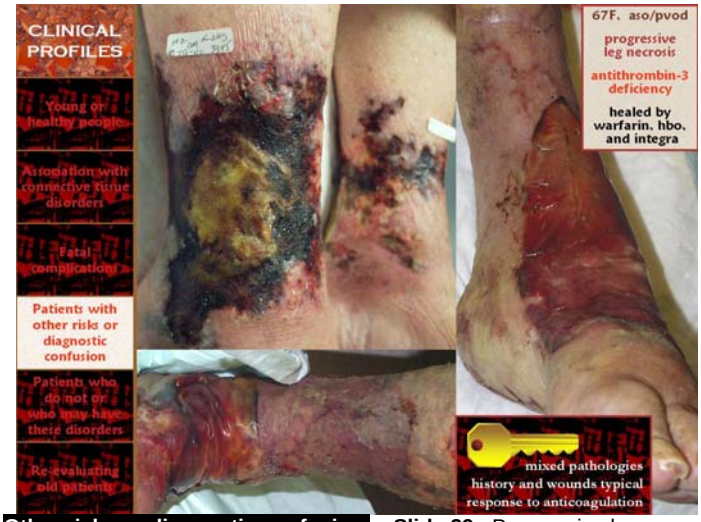


Slide 26 Young woman, lupus, active but controlled. Sudden necrosis leg and thigh skin, then one year hx large ulcer. No response to various care. Also, digital ischemia and fingertip necrosis. Cardiolipin and protein S abnormal. Immediate thorough response to warfarin, ulcer and fingers.

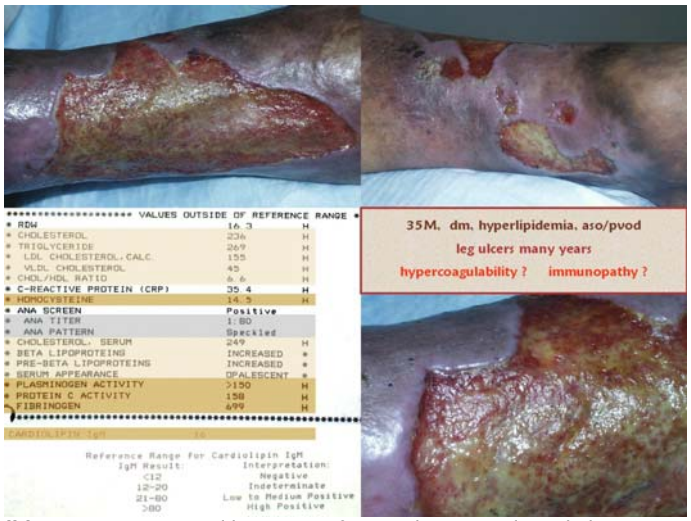


Fatal complications. **Slide 27** Man has diverticular colovesical fistula. Bowel necrosis after surgery. Each of multiple subsequent enterectomies and stomas complicated by bowel and abdominal wall necrosis. Hx finger necrosis after minor trauma; hx dvt. Activated protein C deficient. Died.

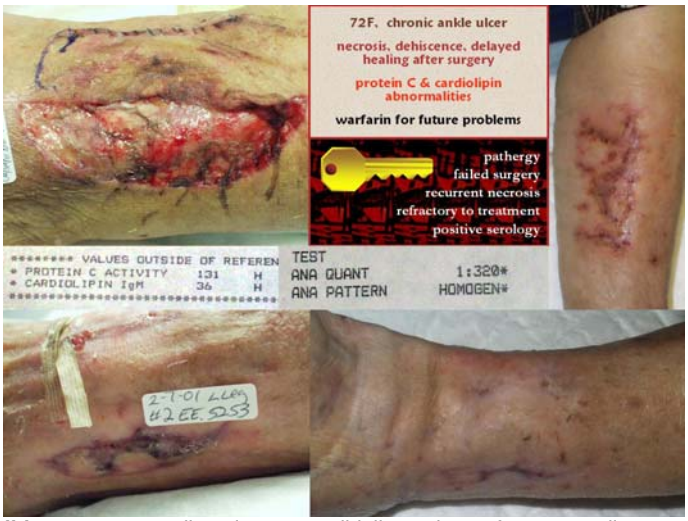
Slide 28 [1] Young woman with fulminant acute lupus. Multiple organ involvement. Extensive necrosis skin and fascias. Protein S deficient. [2] Another pt has coronary angioplasty. Multiple skin necrosis after starting warfarin. Mis-dx and mis-rx as pyoderma gangrenosum. Died.



Other risks or diagnostic confusion. **Slide 29** Progressive leg necrosis, severe pain, typical of ischemia, but necrosis pattern not typical of large vessel disease. Pt does have unreconstructable atherosclerosis, but also antithrombin–3 deficiency. Healed with warfarin-integra-hbo.

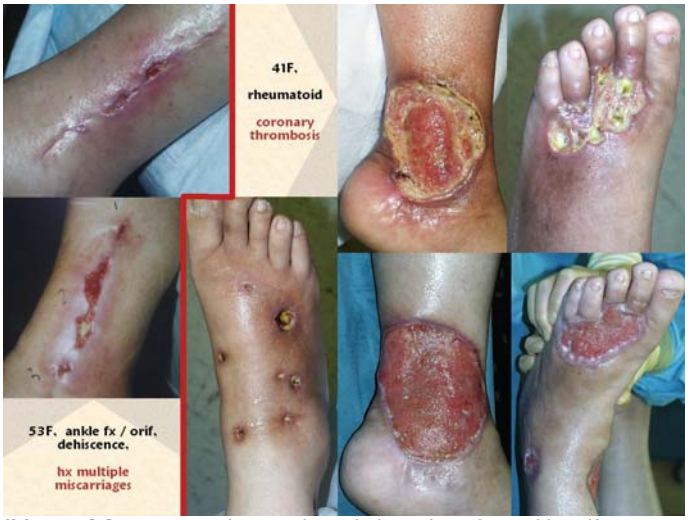


Slide 30 Young man with severe refractory leg necrosis and ulcer. Diabetes, hyperlipidemia, atherosclerosis, but ulcers and lack of response to care not characteristic of any of these. Coagulation abnormalities, and ulcers more characteristic of these diagnoses.

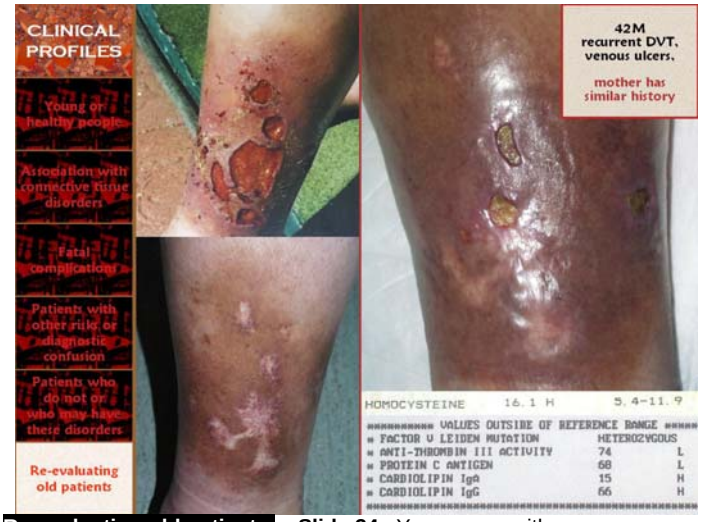


Slide 31 Longstanding ulcer, open tibialis tendon, refractory to all care. Unexpected complications and prolonged healing after surgery. Skin graft donor site with episodic ulceration. Hypercoag w/u done for curiosity only after leg nearly all healed. Would have used warfarin if dx made earlier.

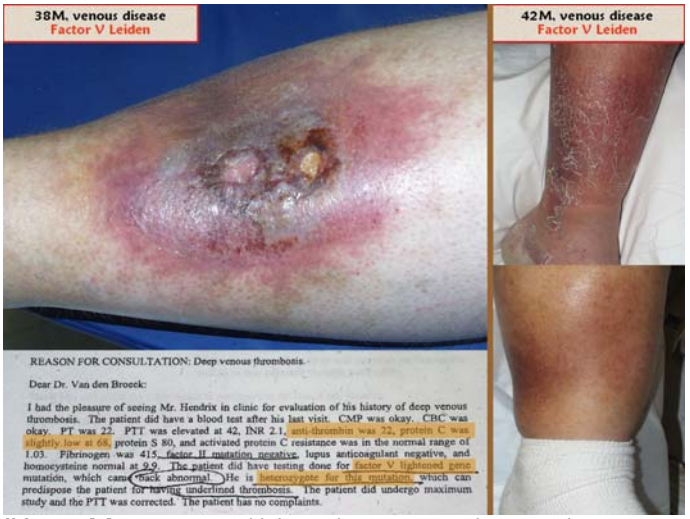
Do not have or may have these disorders. **Slide 32** [1] Patient with venous thrombosis due to iliac vein ligation; no other hx or features. w/u for coag abnormalities not required. [2] Abdominal dehiscence after UGI perforation. Problems due to sepsis, not ischemia; wounds healing.



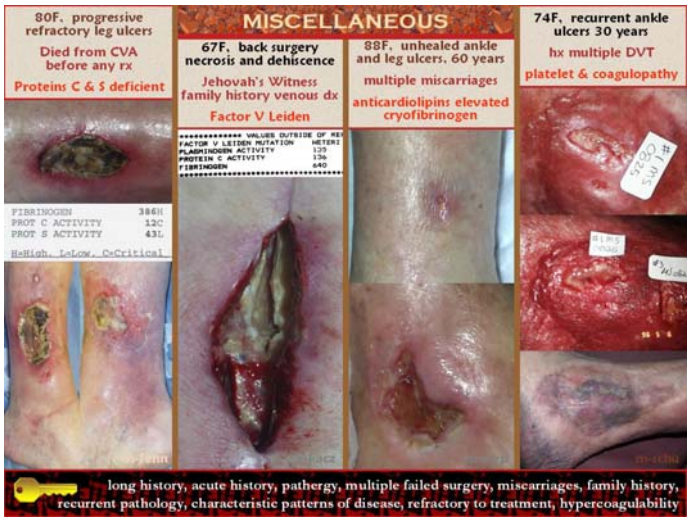
Slide 33 [1] Unexpected necrosis and ulceration after ankle orif. Hx multiple miscarriages. Healed with basics, so hypercoag w/u not done. [2] Rheumatoid ulcers, but refractory to care, suggests other problems. Young patient and sibs died of coronary thrombosis. Hypercoag suspect.



Re-evaluating old patients. **Slide 34** Young man with severe refractory venous ulcers; hx multiple dvt. Healed with basic care. Recent dvt and recurrent ulcer; pt worked up: familial hx, V-Leiden, numerous other hypercoagulable abnormalities.



Slide 35 [1] Young man with intermittent venous ulcer. Work-up on recent recurrence: V-Leiden. Healed with warfarin and other basic care. [2] Young man with intermittent stasis dermatofasciitis, always treated before progressing to ulceration. Work-up on recent recurrence: V-Leiden.



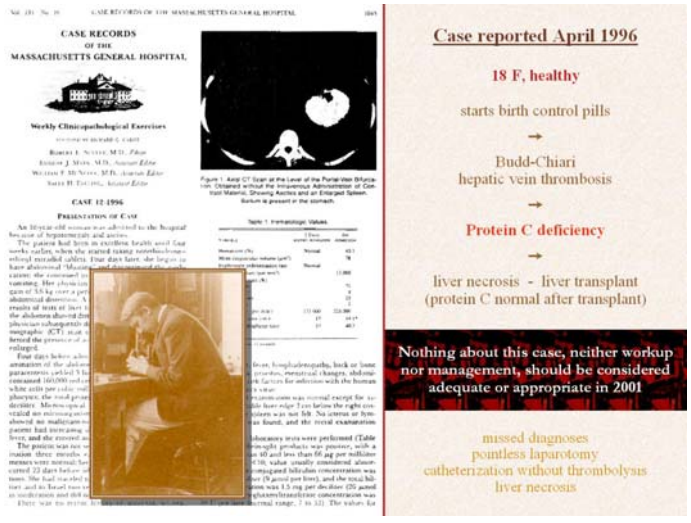
Mix. **Slide 36** A mix of cases, latecomers or incomplete histories, but who otherwise exhibit the features of microthrombotic wounds and the principles of managing them.

[1] 80F, severe painful progressive necrosis and ulceration both legs. Pulses present. Ulcers and necrosis have pattern consistent with immunopathy and/or hypercoagulability, distinct from other common ulcers. Multiple abnormal tests; protein C critically low. Died from stroke prior to any leg surgery.

[2] 67F, rheumatoid, lumbar decompression. Necrosis of fascias and dehiscence of wound for no other apparent reason. Factor V-Leiden heterozygous; other factors with secondary alterations.

[3] 88F, ankle ulcer for 60 years; intermittent other ulcers. No response to years of comprehensive care. Anticardiolipins and cryofibrinogen elevated. Eschewed care for secondary gain.

[4] 74F, refractory ankle ulcers 30 years. Hx multiple dvt, but not a "venous ulcer". Episode fulminant acute necrosis. Free flap died at 11 days, upon withdrawal of anticoagulants. Integra, healed. In retrospect, hypercoagulable; nowadays would work-up, and treat if confirmed.

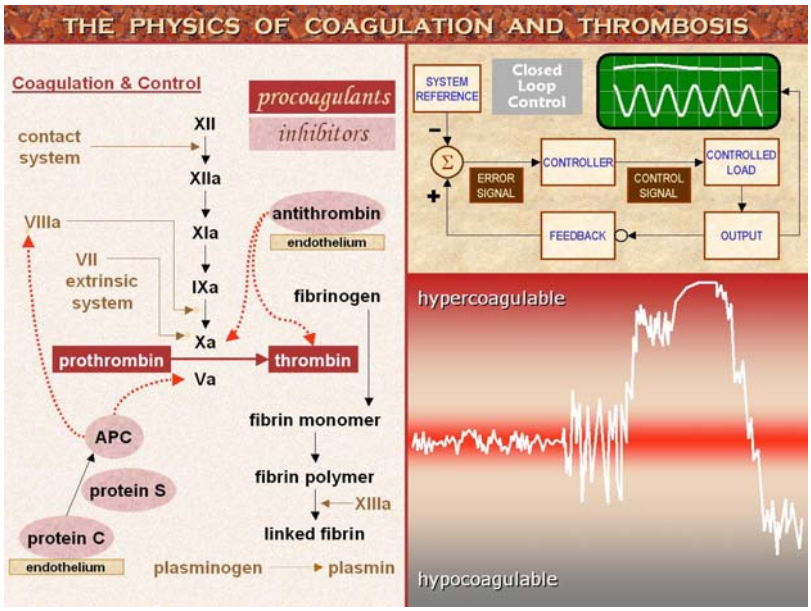


Outside case. **Slide 37** A "Monthly Clinicopathological Exercise" published in the April 1996 *New England Journal of Medicine*.

An 18 year old woman starts oral contraceptives, and within days has abdominal distension (ascites) and pain. After a week or two delay, including a "negative" laparotomy, Budd-Chiari syndrome was diagnosed. Hepatic vein thrombosis was confirmed by angiography, but no attempt was made to extract or lyse the thrombus. The patient slowly progressed to liver necrosis, and ultimately she received a liver transplant. Protein C deficiency was identified as an underlying factor predisposing to thrombosis, which was triggered upon starting estrogens. Protein C levels were normal after implanting the new liver.

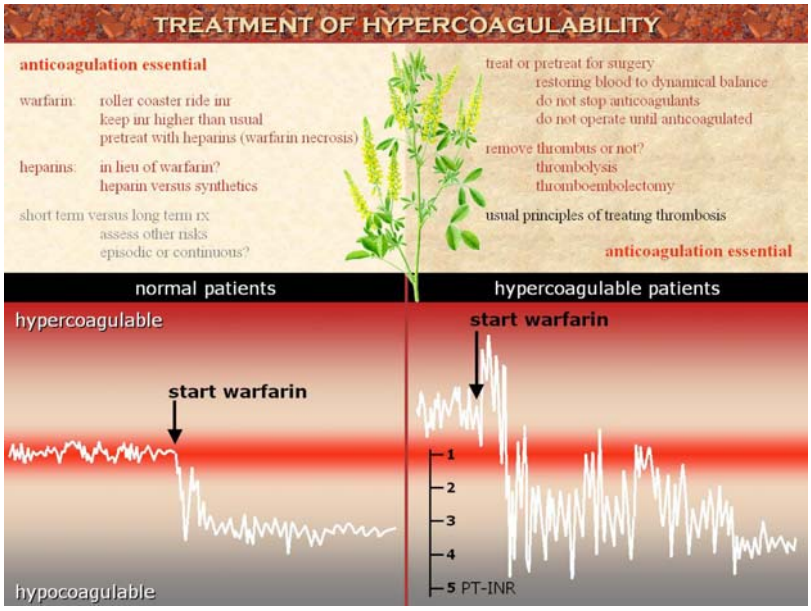
Budd-Chiari syndrome is not news. This case was presented because Protein C deficiency was the cause of the problem. In 1996, missing the hypercoagulable diagnosis and its implications was understandable and excusable, even if managing the hepatic vein thrombosis itself was less than exemplary. In the year 2001, these problems should be considered readily recognizable and manageable.

In the above cases, common features and key concepts emerge: characteristic hx & exam, long hx of disease, long hx refractory to treatment, no other risks for ulceration or necrosis, acute and past / repetitive hx of current problem, single or multiple hx thrombosis or embolism, family hx of these problems, hx miscarriages, association with connective tissue disorders and immunopathies, mixed pathologies and disease associations, other diagnoses resolved or reconciled (eg venous, atherosclerosis), recurrent or multifocal pathology, pathergy after trauma or surgery, single / multiple failed or complicated surgery, history unusual thrombosis or ischemia (patterns, locations, circumstances), progressive or repetitive necrosis-ulceration and amputations, multiple infarctions, characteristic wounds, multiple wound complications, incompetent wounds, characteristic patterns of necrosis and ulceration, gross hypercoagulability, missed diagnoses, missed recognition of microthrombosis, confirmatory histology, confirmatory TcPO2, confirmed coagulation abnormalities, multiple coagulation abnormalities, positive serology, refractory to other rx, no response or failure to heal with basic care, prompt response to or success after anticoagulation, difficulty with anticoagulation, warfarin resistance, wound response to warfarin only, thrombosis or re-ulceration after withdrawal of warfarin, response to hyperbaric oxygen, success with warfarin-integra-hbo. **Suspicion of hypercoagulability is generally based on several (or many) of these features being present in any one patient or characterizing a given clinical event or syndrome.**



SLIDE 38

Having looked at case examples, treatment issues will be looked at again. Understanding the biophysics of coagulation is important. As a non-linear multicontrol system, coagulation is held to its desirable state when the system is healthy. When there are disturbances in the system, this can render coagulation erratic or hypercoagulable or hypocoagulable.

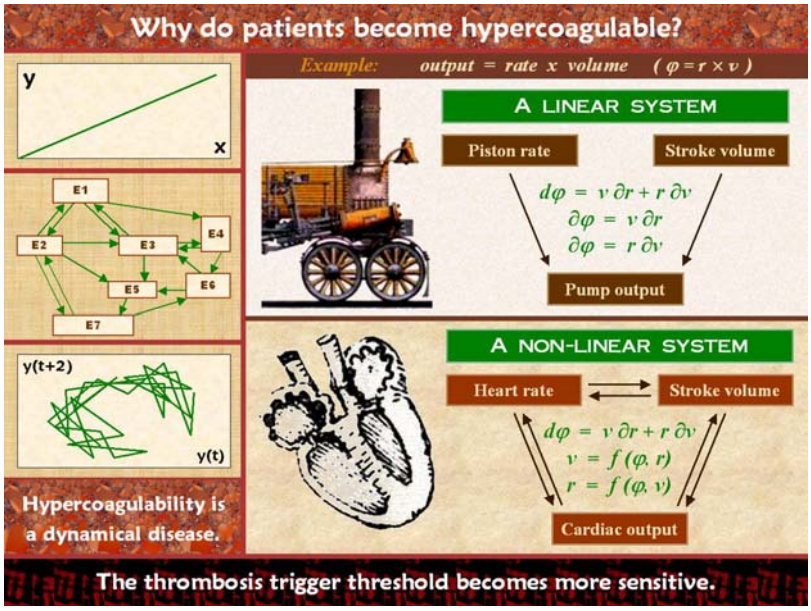


SLIDE 39

Non-hypercoagulable patients who are placed on warfarin can be regulated fairly easily (eg atrial fibrillation, vascular surgery). Hypercoagulable patients can have an unpredictable roller coaster ride with warfarin. Some practical difficulties in managing warfarin in some of these patients makes the use of heparin or synthetics desirable.

Long term treatment or not? Pretreatment for surgery? Thrombolysis or not? these are relevant questions.

If the subject of hypercoagulable or prethrombotic disorders seems new, realize that it is only their role in causing wounds or miscarriages or other common events is what is new. We have had sound principles of treating thrombosis and embolism for a long time. Those principles still apply.

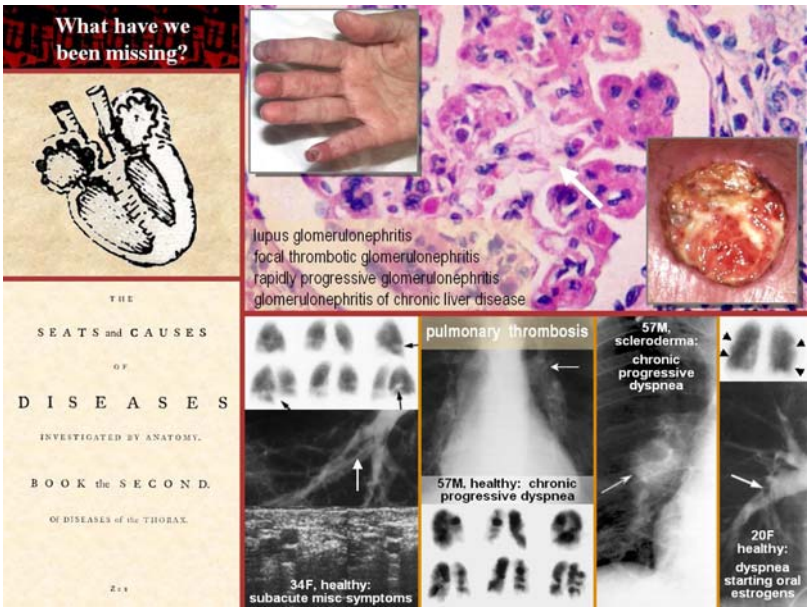


SLIDE 40

Why do patients become hypercoagulable? Even patients with mutant genes (eg factors II, V) are not always hypercoagulable. As with any disease, the simple answer is that one day you are healthy, and then you are not. However, the biophysics and dynamics of these disorders do offer an explanation.

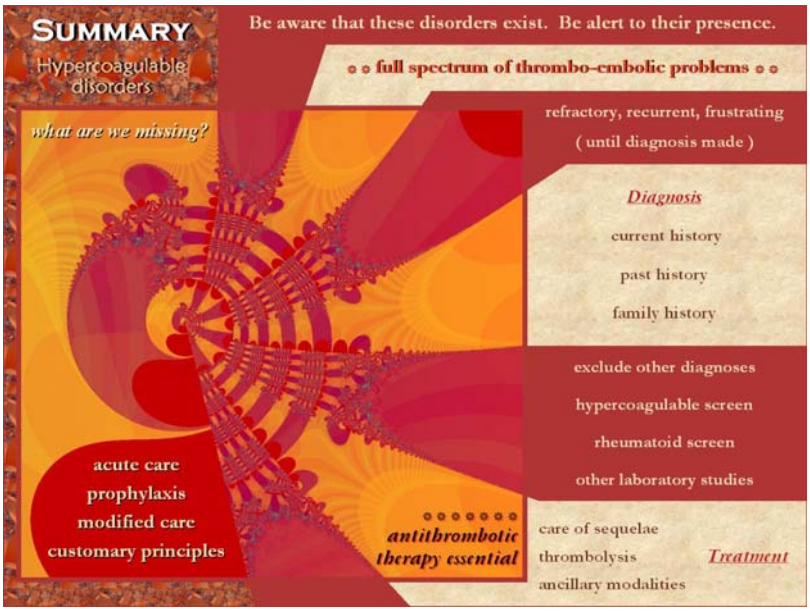
Non-linear systems are subject to certain behaviors and alterations. Physiology and medicine have traditionally looked at and explained pathology based on linear relations between any two variables (other branches of science are decades ahead of medicine in this regard). As a complex multicontrol system, the dynamics of coagulation can only be described by methods applicable to non-linear systems. What this means is that small perturbations in the system, due to age, disease, drugs, and various transient alterations can intermittently have small or major effects on the output of the system. Hypercoagulable thrombosis is a “dynamical disease”.

The net effect is that age, disease, and degeneration can make the trigger for thrombosis more sensitive, so that thrombosis occurs spontaneously or prematurely under conditions when it is ordinarily balanced not to do so.



SLIDE 41

It is easy to look back on old patients and realize that they could have had better care had we only understood this problem earlier. It is also to be assumed that hypercoagulable states affect more than just the gravid uterus, deep veins, and leg skin (the hypercoagulable sequelae that are now commonly recognized). Assume for a moment that microthrombosis occurs episodically in the lung, eventually leading to cor pulmonale. This would currently be misdiagnosed as recurrent "pulmonary emboli" even absent any evidence of venous thrombosis. The same is possibly true in the kidney. If one extrapolates a predicted pathophysiology, it seems like it should be similar to the non-immunopathic forms of glomerulonephritis. Perhaps some forms of lupus "nephritis" are really thrombotic problems. Perhaps chronic renal failure in some lupus patients can be prevented by anticoagulation. Remember, for years we "knew" that digital ischemia was due exclusively to vasospasm or vasculitis, although the problem often did not resolve with treatments for such. For years, we were certain that every leg ulcer was due to venous disease, old dvt's, vasculitis, or the lupus itself, even though there was no evidence nor did the ulcers improve with specific therapies. Now we know otherwise. What have we been missing? What are we still missing?



SLIDE 42 SUMMARY

Hypercoagulability occurs, leading to acute and chronic, overt and subtle syndromes due to macrothrombosis and microthrombosis. Some hypercoagulabilities result from unequivocal genetic alterations; some result from a relative imbalance of these factors – a dynamical disease. With regard to the soft tissue pathologies which result, they are frustrating to treat and refractory to care until the correct diagnosis is made. Differential diagnosis is suspected based on the active clinical events plus past medical history and family history. Laboratory studies can confirm the diagnosis. Workup should include a screen for immunopathies since the two sets of disorders can occur concomitantly.

Treatment focuses first on the active clinical syndrome or sequelae of the hypercoagulable state. Thrombolysis should be considered in life-and-limb threatening conditions. The quintessential treatment is anticoagulant therapy. Once acute therapy is started and acute illness is stable, one must decide the duration of antithrombotic therapy; lifelong therapy may be required in select cases. It is suggested that hypercoagulability has more protean manifestations than heretofore recognized, and these problems should be elucidated.

SLIDE 3 Sidebar

In 1569 and 1571, Dr. Nicolas Monardes of Seville published 2 volumes documenting discoveries from the New World. Emphasizing botanicals of medicinal and potential commercial value, the work was translated into English in 1577 by merchant John Frampton under the title **Joyfull newes out of the newe founde worlde**. Illustrated is Monardes' original illustration of El Tabaco. Tobacco's current bad rap aside, it was the preeminent medicinal herb of the native Americans, good for many things, including curing wounds and ulcers. It was also good for bleeding, in Frampton's words:

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

Every folk, cultural, and educated or official materia medica ever codified has entries or agents concerning the staunching of blood, be it from wounds or body orifices. The significance of bleeding and the need to stop it were obvious. However, the prevention of coagulation did not become an issue until just 100 years ago. Considering that vascular surgery was not formally developed until 90 years ago, and that coronary artery thrombosis and myocardial infarction where not documented in English until 1912 – yes, 1912 - (Heberden described angina pectoris in 1768, but there was no appreciation of myocardial infarction until the report by James Herrick of Rush Medical College, published in *JAMA*), there was never a reason to seek anticoagulants until recently.

SLIDE 6 Sidebar

Cosmas and Damian were Persian brother physicians, martyred by Diocletian in 278 AD. Recognized by the Catholic church for their accomplishments, they are now the patron saints of surgery. One of their posthumous miracles is that they transplanted the leg of a recently deceased Moor onto the chronically ulcerated leg of a patient, illustrated here by the Schwäbische Master of the Schnaiter Alter, c1500. Working in the eastern Mediterranean, chances are good that the leg ulcer was due to thalassemia or other hemolytic anemia, well-documented causes of refractory ulcers.

In lieu of miraculous surgery, treatment for leg ulcers at the time consisted of available medicaments such as frankincense, illustrated here in a woodcut from the Gerard-Johnson Herbal. Aromatic plant resins were luxury commodities and cherished gifts in ancient world commerce. Frankincense and other balsamic saps were also some of the premiere vulneraries (wound herbs) of the time. In use well before recorded history, many ancient authors wrote about these resins for wound care. They are in the Smith and Ebers Papyri, and myrrh alone is prescribed 54 times by Hippocrates, not all, but many for the treatment of wounds and sores. Even today, these resins are in many hospital pharmacies, including tincture of myrrh. For years, balsam of Peru was listed in the United States Pharmacopoeia (USP), styrax (Liquidamber, sweet gum) remains USP, and benzoin is in the National Formulary (NF). These resins are sweetly scented, emollient to open tissue, strongly antibacterial, and they do not decay, making them a useful adjunct to bathing and dressing for the daily management of wounds. In the pre-modern era, when wound debridement and hygiene were little understood or practiced, these were valuable antidotes to wound putrefaction.

Go up into Gilead and fetch balm, O virgin people of Egypt. You have tried many remedies, all in vain; No skin shall grow over your wounds. — Jeremiah, 46:11

The mid 16th through the 17th centuries, the epitome of the renaissance that founded our principles of scientific thought, investigation, and education, was also the era of the great herbals. While some of these botanical encyclopedias were written by "naturalists", most were written by physicians, because these were the pharmacopoeias of the time. Remember that the first commercial synthetic drug was aspirin, in the latter 19th century, and the modern pharmaceutical industry evolved only after that. Until then, important drugs all came from natural sources, and botany and pharmacognosy were standard medical school courses well into the 20th century. The great herbals were pharmacy textbooks. In 1597, the preeminent surgeon, superintendent of gardens, and herbarist to kings, Dr. John Gerard, published a compendium of botanical knowledge. Gerard's own first edition simply copied text from other uncertain sources. Combined with many errors of his own, it was neither correct nor erudite, but it became very popular. In 1633 Thomas Johnson, an apothecary and botanist, was commissioned to undertake a massive revision of the book, including thorough updates and corrections, more accurate illustrations, and many new entries. Scholarly and highly regarded, the 1633 Gerard-Johnson edition, **The Herball or Generall Historie of Plantes**, became for generations the premiere English source of medicinal information. If you love botany, medical history, or old books, the Gerard-Johnson 1633 herbal is available in a huge facsimile reprint from Dover publishers.

SLIDE 7 Sidebar

This is the view of a lab at the Norwich Pharmacal Company, early 20th century. The time of this photo might be considered the midpoint of a golden century of biochemistry. Friedrich Wöhler's 1828 synthesis of urea, and Friedrich Kekulé's 1858 insight of carbon tetravalency, along with his 1865 realization of the benzene ring, are symbolic markers of the advent of biological chemistry. Watson and Crick in 1953 mark the start of "big" biochemistry. Between these bookends, science elucidated huge amounts of crucial knowledge about the chemistry of plants and animals, along with laboratory and investigational methods that promise to be with us for a very long time. However, in investigating medical and scientific history, authors, teachers, and historians tend to retell the stories of the big players, the romantic adventures, and the big concepts that capture the public's fancy. Figuring out the Kreb's cycle or the cytochrome system doesn't seem to sell books, so the story of how human biochemistry was researched and mapped is somewhat apocryphal, even though it is so recent. Whoever these anonymous explorers were, they toiled in labs like the one shown, in universities and pharmaceutical companies, and still do, to understand how our molecules work. The main sequence of the coagulation system was largely pieced together by the end of this era.

SLIDE 8 Sidebar

In this diagram of the technique of vascular anastomosis, note the initials A.C. The turn of the 19th century saw a flurry of interest in organ transplantation. Although Landsteiner elucidated the ABO antigens of blood in 1901, the immunological barrier to allogeneic organ grafting was yet to be recognized or understood, nor could it be until there were practical surgical techniques for organ revascularization. Several incidental vascular operations were reported in the last decade of the 19th century. In 1902, Alexis Carrel illustrated his technique for vascular anastomosis. He developed consistent methods and tools for this purpose, following which he published many papers describing the techniques of organ grafting and revascularization. In 1912 he won the Nobel prize in medicine and physiology, the first American to do so, for this seminal work establishing the art and science of vascular surgery. Even so, vascular surgery developed slowly, with many wrong turns along the way. The two paradigm procedures of peripheral vascular surgery, the femoral artery bypass and the abdominal aortic replacement, were first reported in France in 1948 and 1952. Managing thrombosis has been integrally bound to vascular surgery for nearly 100 years, and anticoagulant therapy has been a part of the art for 60 years, but it is only in the past few years that we have realized that intrinsic coagulation abnormalities can subvert the best vascular operations or efforts to modulate blood clotting.

SLIDE 9 Sidebar

Under the auspices of the army, the vast experience and medical records of Civil War surgery were accumulated into the 6-volume **Medical & Surgical History of the War of the Rebellion**, published 1870-1888. It was considered by Europe to be America's first substantive medical opus. The sullen soldier shown here comes from Volume 2, 1877, from a painting by Edward Stauch of the Army Medical Museum. He suffers "hospital gangrene" after gunshot wound amputation. These events came on the eve of the great elucidation of the cause and prophylaxis of infections. More than a century later, the principles of treating and preventing infection have been largely mastered. Septic infarction of injured tissue is now the infrequent exception. Infarction due to macrovascular insufficiency or traumatic vascular sequestration has also been understood, to one degree or another, for some time. Inflammation as a cause of tissue infarction has been clarified more recently. Yet in modern surgical and medical practice, we still see instances of peculiar tissue necrosis which cannot be attributed to these mechanisms. Hypercoagulability is proving to be the category of illness which explains many of the heretofore perplexing instances of soft tissue necrosis.

SLIDE 10 Sidebar

The diagnosis of hypercoagulability must be confirmed by laboratory tests. We can measure so many different things in biological materials that it is easy to forget that this was not always so. For a very long time, the only exam that resembled the clinical laboratory was the practice of uroscopy, and this was an essential practice for physicians from the middle ages through the renaissance and beyond. Uroscopy flasks (matulae) were used for these exams. Not only do many paintings and illustrations of the times confirm the practice, but the matula was the most recognizable logo of the medieval physician. Uroscopy wheels (matula disks) such as the one shown here (Udalricus Binder, **Epiphaniae medicorum, Speculum videndi urinas hominum**, 1506) were published in many medical texts, sometimes hand-tipped with appropriate, semi-standardized urine colors. They were a system for measurement, a chart of colors and characteristics by which the physician could judge what was wrong. Test-Tape was unheard of, but Taste-Test

was mandatory. Even with the advent of real chemistry and pharmaceutical practice in the latter 19th century, clinical measurements remained cumbersome, laborious, expensive, and inaccurate. Technological tools were mandatory to allow clinical laboratory services to become as pervasive and as pertinent as they are today. Wallace Coulter's electrical particle counter for blood cells was developed in 1957, and automated chemistry appeared at the same time. In the words of one author "... the arrival of the AutoAnalyzer helped to transform the clinical chemistry laboratory from a repository of historical data into a control center for aiding in diagnosis and the treatment of patients."

SLIDE 11 Sidebar

Throughout history, medical texts have used certain standardized graphical figures. The "wound man" is one such archetype of illustration, especially prominent in renaissance works. The intent was to show common types of injury, usually penetrating wounds from military weapons. The one illustrated here is the title page illustration from **Dis ist das buch der Cirurgia, Hantwirckung der wundartzny**, by Hieronymous Brunschwig, a lifelong military and wound surgeon from Strasbourg. This 1497 book compiled ancient and medieval knowledge with his own experience. Later and more prominent books, such as Hans von Gersdorff's **Feldtbuch Der Wundartzney** (a 1517 military surgeon's wound manual), were more lavishly illustrated, with more beat up mo' better wound men. Nevertheless, Brunschwig's **Cirurgia** was the first important surgical text printed in German, the most illustrated surgical text up until that time, and the first detailed account of gunshot wounds. It went through many editions and was popular well into the 16th century.

Even today, the "wound man" figure is, in the minds of many physicians, a conspectus of wound diagnosis. The notion of "wound diagnosis" seems almost a malapropism – what is there to diagnose? A wound is a traumatic condition, self-evident in origin, right? This may be true to an extent, but there are also chronic wounds. Surgeons take wound repair for granted – it is what lets them get away with doing surgery – but there are times when this basic biological machinery is impaired. When the infrastructure of repair is incompetent, the results are complications of trauma and surgery and chronic non-healing ulcers. A thorough wound diagnosis has a number of components, but tracking down the cause of the impairment is crucial. In addition to the more commonly recognized causes, such as arterial insufficiency or pressure or immunopathy, the many forms of microthrombosis are now recognized as a significant cause of chronic ulceration and wound healing impairment.

SLIDE 14 Sidebar

Dr. Thomas' Eclectric Oil, made with electricity, was capital for burns, bruises, and just about anything else what ailed you. Other manufacturers also made eclectric oils, and all manner of bizarre concoctions, therapeutic claims, and advertising gimmicks are to be found on similar trade cards. These trade cards, still easy to come by at swap meets and flea markets, are the ephemeral documentation of a once flourishing patent medicine trade during the latter 19th century. Concurrently, a legitimate ethical scientific drug industry was arising as the offspring of some pharmacists and some industrial chemical companies. By the turn of the century, most of the major pharmaceutical giants had been established in Europe and the United States. With the concomitant rise of our current system of medical education, an explosion of medical technologies and science, and the foundation of a true scientific approach to pharmacy and drug development, it was obvious that the silly pretentiousness of the patent medicine trade would have to come to an end. Indeed it did, when Congress passed the Pure Food and Drug Act of 1906, establishing the US FDA. Of course, the patent medicines never really disappeared, and there is currently a resurgence of interest in using and making money off of herbal and alternative medications. Throughout the glorious patent medicine era, there were never any patent medicine claims about treating blood coagulation. By the time anybody earnestly realized that controlling coagulation was a desirable goal, we were well into our current mode of scientific medicine and pharmacy, and the patent medicine era was already gone by a decade.

SLIDE 15 Sidebar

Most modern doctors tend to pooh-pooh the practices of the patent medicine era, but such practices remain within organized medicine. While some specialties such as cardiology or nephrology are extremely well developed in terms of basic science underpinnings and technological therapeutics, other subjects remain poorly understood or untaught. Soft tissue pathology and the biology and therapeutics of repair are one such area. During the era when pharmacists compounded the doctor's prescription, mullein was a common ingredient for soft tissue problems. The common mullein, Verbascum thapsus, naturalized from Europe, and found throughout the temperate United States (the photo here was snapped along the Mogollon rim), has a long medicinal history, suitable for wounds, swellings, inflammation, and the like, and possibly the best remedy ever for the piles.

While there was little science behind most herbal medicine, ***many*** of these drugs had some basis in legitimate empiric observation. Some even received scientific scrutiny, and digitalis, cinchona, opium, belladona, coca, and many others, along with their derivative chemicals, are the living legacy that we have from pre-modern medical practice. In contrast, we are so ready to accept as gospel anything in a commercial medicinal bottle, that we overlook that there is hardly even any empiric legitimacy to some of the "wound remedies" that circulate through modern hospitals and physicians offices. While products like those illustrated have some benefit for symptomatic relief, they have no affect on physiological and pathological processes, but this does not prevent vendors from making or implying such claims. The truth though is that there is basic science behind soft tissue and body infrastructure pathology. We are learning to recognize the diseases and treatments. Hypercoagulability and its affects on soft tissues and injury is one such area of current development.

SLIDE 37 Sidebar

Speaking of venerable old institutions . . . this is a photo of an unidentified student in the lab at Johns Hopkins Medical School, circa 1915. Jay McLean was one such student, who as a sophomore in 1916 was doing a project to identify tissue thromboplastins. Instead, he identified a tissue anticoagulant. Especially abundant in the liver, it was called heparin. Its potential as a therapeutic agent was perceived immediately, but it was not until 10 years later that it could be sufficiently concentrated to attempt clinical administration. The first attempts at intravenous administration turned out to be too toxic for further use. The Canadian Charles Best (best known for his association with Frederick Banting, together having isolated insulin in 1921), tackled the problem. Along with colleagues, the lung and other organs were identified as richer sources of heparin, and by the late 1930s a sufficiently purified and standardized drug was ready for regular prescribing. By then, the concept of pathological intravascular thrombosis was well understood in its many manifestations. The first clinical report of heparin usage was by Crafoord, in *Acta Chirurgica Scandinavica* in 1937, for the prevention of venous thrombosis after surgery.

SLIDE 39 Sidebar

Pictured is Melilotus officinalis, one of the Sweet Clovers. Its medicinal properties were described by the ancient Greek herbalist Dioscorides, and Gerard (see slide 6 sidebar) gives a thorough explanation, including its uses as an anti-inflammatory and wound healing agent:

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

Naturalized to the western hemisphere, cattle in certain parts of the U.S. and Canada developed "sweet clover disease", described in the 1920s, a fatal hemorrhage from eating improperly cured sweet clover hay. The characteristic sweet odor of these clovers, the odor of new-mown hay, comes from a glycoside called coumarin, still used as a flavor and fragrance in foods and perfumes. The hay turns bitter as it is dried, and the bitter taste and the hemorrhagic properties were both traced to a chemical change in coumarin. The responsible derivative, bishydroxycoumarin (dicoumarol), was finally identified and synthesized in the early 1940's. Its potential use as an anticoagulant was already envisioned, and by the late 1940s, dozens of clinical trials had been reported in medicine and surgery. There was concurrent interest in quantifying coagulation, and by 1950, our current concepts of short and long term anticoagulation with heparin and individualized dicoumarol dosing were established. However, the full utility of these drugs was yet to be realized, and as of 1950 these drugs were still listed as unofficial new remedies. They moved up through the ranks of NF and USP over the next decade. By 1960, Quick's "prothrombin time" proved to be the most practical way of monitoring therapy with the coumarin glycosides. Of the hundred or so synthetic coumarins which were tested, warfarin came to dominate as the common clinical agent.

SLIDE 41 Sidebar

Circa 1489-1513, Leonardo da Vinci made thousands of anatomical drawings, including this study of the heart. Most of his drawings were of exceptional detail and accuracy, but Renaissance medicine was so influenced by the inaccuracies of traditional Galenism that even Leonardo consistently erred in rendering parts of the heart and central vessels. He described systole and diastole, precisely drew the cardiac valves, and understood the advantages of 3 cusps, but he never understood how blood circulates. This would await William Harvey's **Exercitatio Anatomica De Motu Cordis et Sanguinis in Animalibus** ("**De Motu Cordis**") in 1628.

In 1761, Giovanni Battista Morgagni published his magnum opus, **De sedibus et causis morborum per anatomen indagatis**, quickly translated and published in English in 1769 by Benjamin Alexander, M.D. as **The Seats and Causes of Diseases Investigated by Anatomy**. As professor of anatomy and president of the University at Padua, Morgagni succeeded Vesalius, Fallopius, Fabricius, and Spigelius. He spent a lifetime dissecting post-mortem cadavers, studying applied anatomy and disease. Prior to Morgagni, disease was understood to be a consequence of altered humours, a body of knowledge carried from ancient times through Galen. After Morgagni, we understood the anatomical basis of pathology. Morgagni is the uncontested father of pathology. But just as Leonardo could not see what was directly before him, blinded by an inculcated structure of erroneous prior knowledge, so too Morgagni missed some of what we now would consider blatantly obvious.

In Morgagni's day, blood was understood to clot as a method to staunch bleeding. Men of medicine sought remedies to stop bleeding when nature failed in this task. Thrombus was also obvious as a post-mortem change, and well described by Morgagni in its many variations. But blood was not understood to clot in the living system, so when Morgagni observed it, he neither recognized nor understood it. **De sedibus** was published in the form of personal letters to an unidentified (perhaps fictitious) friend. Seventy such letters were grouped by body part into five books. Each letter has numbered articles, each essentially an autopsy report. Letters 2 – 5 of Book 1 describe apoplexy. Letters 26 and 27 of Book 2 (whose title page from Alexander's translation is illustrated here) describe sudden death due to diseases of the great vessels and heart. In these letters, Morgagni describes various details of stroke, ruptures and dissections of aortic aneurysms, valvular heart disease, congenital heart disease, and he even correlates post-mortem findings with pre-mortem symptoms of dysrhythmia. Atherosclerosis is described abundantly as the "bones" of the heart and vessels, in the form of bony scales and valves. In Article 2 of Letter XXVII, he autopsies a 75 year old woman whose findings can only be interpreted as a myocardial infarction with left ventricular rupture. In all of these cases, post-mortem thrombosis is obvious, being the serum and grume which he had to remove to see the more important parts, but nowhere does he acknowledge pre-mortem intravascular thrombosis.

Morgagni accurately observed vascular pathology, but he misinterpreted its physiological implications. As he saw the problem, the bony scales of the vessels could become large enough to occlude blood flow, or perhaps they functioned as valves or they eroded the vessels. Much of his interpretation is valid, but his attempts to attribute hemodynamical consequences and mortality to these bones at times becomes convoluted and contrived, forcing a square peg of misinterpretation into the round hole of reality. Why then could this highly intelligent and observant man not see what every educated person today takes for granted? Harder yet is to realize that coronary thrombosis was not revealed to the world until 1912 (by Herrick, see slide 3 sidebar). What will future generations think of our medicine? What will they take for granted, and scratch their heads pondering how it is that we missed so much of what should have been obvious?

END

Hypercoagulability: Prethrombotic and Microthrombotic Disorders

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