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
Phoenix, AZ

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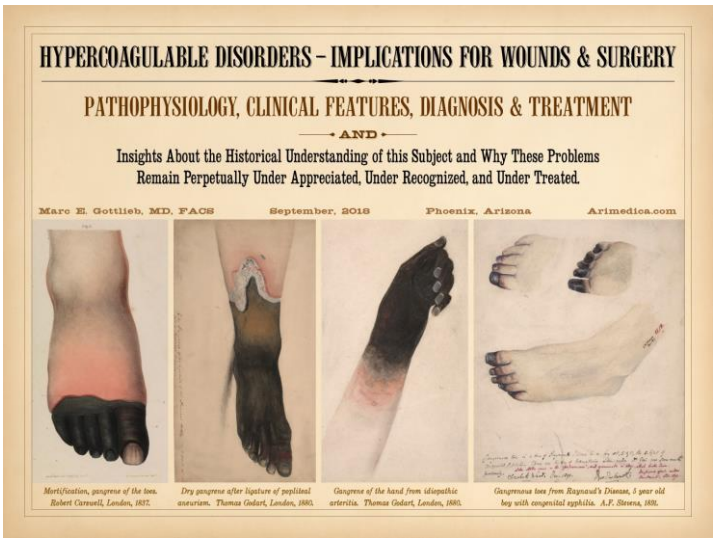

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Hypercoagulable Disorders – Implications for Wounds & Surgery
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Insights About the Historical Understanding of this Subject and Why These Problems Remain Perpetually Under Appreciated, Under Recognized, and Under Treated.

This presentation was given on September 27, 2018, in Phoenix, Arizona, a grand rounds presentation for the Department for Surgery. It is on the subject of the hypercoagulable disorders, and especially their implications for surgery, surgical complications, and acute and chronic wounds. After introductory cases, the presentation has three main sections. First is a review of the basic clinical features of these disorders, including pathophysiology, clinical presentations, diagnosis, and treatment. The second and third sections address the issue that these disorders are prevalent, morbid, and clinically important but nonetheless poorly understood or recognized by most physicians. The second section examines the historical basis of why thrombotic disorders and anticoagulation therapies came late to medical knowledge. The third section examines the physical and physiological basis of why these disorders can behave in non-obvious ways which further confuse their understanding and appreciation.

This presentation and case studies by Marc E. Gottlieb, MD come from his practice of reconstructive plastic surgery in Phoenix and Scottsdale, Arizona. This presentation is available for viewing and download at Dr. Gottlieb's website ***arimedica.com*** which is used solely for the posting of presentations and other academic and instructional materials.

Mortification, gangrene of the toes. *Robert Carswell, London, 1837. This is an image a common disorder, vascular gangrene of the forefoot, most likely a thrombotic or embolic complication of atherosclerosis or related vascular disorders. A coagulation disorder could coincidentally be present, but the ordinary implication is that common vascular disease is the cause.* ***Dry gangrene after ligature of popliteal aneurism.*** *Thomas Godart, London, 1880. Acute popliteal artery interruption, untreated, is apt to cause gangrene of distal leg and foot. Whether from atheromatous disease, aneurysm, or trauma, the problem nowadays is easily fixed by surgical or thrombolytic interventions. In 1880, there was no treatment except amputation. In any epoch, the implication is that this is due to macro-vascular disease, not a disorder of thrombosis.* ***Gangrene of the hand from idiopathic arteritis.*** *Thomas Godart, London, 1880. This infarct of wrist and hand is attributed to "idiopathic arteritis". A variety of underlying primary diagnoses could be present, but lupus or scleroderma and their distinctive fibromuscular acral arteriopathy is the likely cause. While this is indeed a vasculopathy which can render vessels thrombogenic, it is also likely that there is a concomitant hypercoagulable disorder which adversely interacts with the altered vessels.* ***Gangrenous toes from Raynaud's Disease, 5 year old boy with congenital syphilis.*** *A.F. Stevens, 1891. "Raynaud's" implies intermittent transient ischemia due to an irritable spasticity of arteries, but Raynaud's per se never causes infarction. In adults, the disorder usually implies lupus or scleroderma, and by the time that actual ulcerative or infarctive complications occur, the vessels have the distinctive anatomical pathology of lupus-scleroderma arteriopathy. In children nowadays, acral gangrene is most often associated with purpura fulminans in the face of life threatening infection, but the implied disorder here is a slow chronic problem. Embolic complications of syphilitic aortitis is distinctly possible, and in that era it would have been not uncommon, even in pediatric patients. However, whenever an odd or unlikely thrombotic or ischemic event occurs, in unlikely demographic groups, under unlikely circumstances in the absence of vascular disease, or as a chronic or recurring problem, the micro-thrombotic and hypercoagulable disorders must move to a prominent position in the differential diagnosis.*

These illustrations are from 19th century British sources. ***Robert Carswell*** *(1793-1857) was a Scottish pathologist. His most famous work is "Pathological Anatomy : Illustrations of the Elementary Forms of Disease" (1837), a large opus which includes 2000 watercolor drawings he made of diseased organs and tissues. The illustration here of a necrotic forefoot is from Plate II of the chapter "Mortification".* ***Thomas Godart*** *(1821-1887) worked in London at the Pathology Museum of St. Bartholomew's Hospital. This museum of pathology specimens began circa 1726 for the purpose of research and student education, and it became one of the world's most preeminent collections of pathological materials. Its "Pathology Illustration Collection" dates to 1844. He served 1852-1887 as its second curator and librarian, and also its resident Museum artist, preparing many images of clinical or pathological conditions that could not be directly preserved.* ***Algernon Francis Stevens*** *painted the image of necrotic toes (1891) while a student at St. Bartholomew's Hospital Medical School in London. (He was later noted for his duties in the Indian Medical Service.)*

To the reader: **It is suggested** that while reading this annotated version, that the presentation file be opened simultaneously so that the images can be viewed in high resolution with full visual detail. These files can be accessed from the Presentations page or from the direct links:

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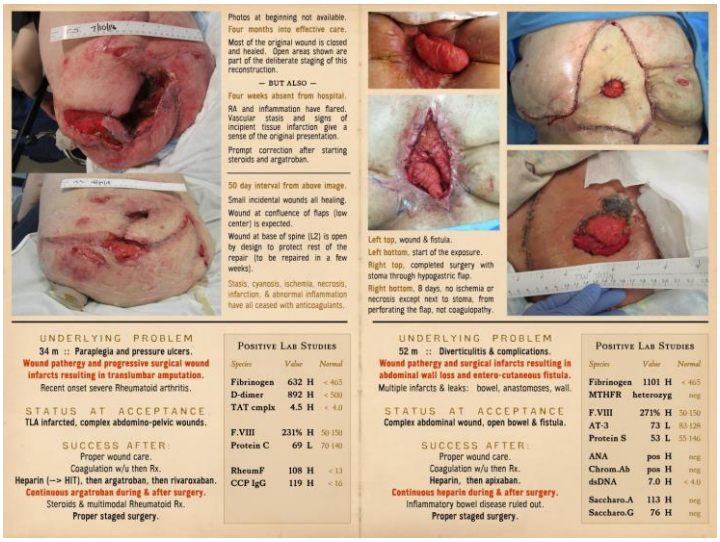

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Introductory Cases

Here are two introductory cases that illustrate the pernicious effect of hypercoagulable disorders to cause complications of surgery, and in turn profoundly affect patients' lives for the worse. In the author's practice, there is nothing unusual about these two cases. They were selected solely because they were recent cases, still actively under care, thus prompting the interest in having a Grand Rounds on this subject, and because there are pictures available to illustrate them.

Case #1

This is a 34 year old man, paraplegic from trauma 15 years ago, who recently developed pressure ulcers. Surgery for the ulcers was complicated by flap and wound necrosis. This began a circular set of operations and complications that resulted in progressive "debridement" until the patient had had trans-lumbar amputation. TLA is an operation legitimately done for pelvic sarcomas, but not for other reasons. The progressive problems were a tipoff to an underlying inflammatory or vascular or coagulopathic disorder, and surgery should have been suspended long before the patient got into this desperate life-altering state. In addition, during this interval of aggravated surgery, he developed severe sero-positive rheumatoid arthritis affecting the shoulders, elbows, wrists, and hands, a crippling disorder for him. When request was made for transfer and assumption of care, the diagnosis, sight unseen, was of a primary hypercoagulable disorder with secondary auto-immune disorder. This was readily confirmed on acceptance of the patient and relevant workup.

Highlights of the workup revealed high levels of fibrinogen, d-dimer and thrombin-antithrombin complex as reflex markers of a hypercoagulable state, high factor VIII and low protein C as hypercoagulable species, and high rheumatoid factor and anti-CCP confirming rheumatoid arthritis. He was started on intravenous heparin drip and multi-medicine treatment for RA. Within 2 weeks, there was a sudden drop in platelet count and a rise in PF4 antibodies consistent with heparin induced thrombocytopenia (HIT), so he was switched to intravenous argatroban. Subsequently, he would be on argatroban starting a day before any surgical procedure then for about 10 days hence, and then between cases he would be on an oral direct thrombin inhibitor (rivaroxaban). Proper topical wound care started as well.

There are no photographs of the original presentation or admission, but the entire trans-lumbar amputation was a large open wound with areas of fascial and skin necrosis, plus necrosis of the lower spine (the amputation had errantly been done at L4-L5 level thus causing pressure necrosis there). Wound closure was done incrementally with delayed flaps and staged transfers. After 3 months, the majority of the wounds were closed, and all of this happened without any flap necrosis or wound infarcts. At that point, the patient had necessity of returning home for a while, during which RA therapies, rivaroxaban, and topical care for the remaining wounds were to be conducted at home.

The first photograph is the appearance after a 4 week hiatus at home. Despite the seeming problems, this wound is substantially smaller than original presentation. However, rheumatoid has flared up severely, and the flaps show a degree of inflammation, vascular stasis, and focal ischemia not present at the time of hospital discharge, and now consistent with the dual autoimmune-hypercoagulopathic pathology affecting the wounds. He was readmitted to the hospital for aggressive control of those pathologies, including a return to higher doses of anti-RA meds, and return to IV argatroban. The second image shows appearance after 50 days and one further operation. All signs of active pathology are subsided. Small incidental superficial wounds are healing properly. The lower central wound has the typical minor dehiscence expected at the confluence of flap tips and is now healing. The upper central wound is at the base of the spine (now amputated at the proper level L2-L3), left open deliberately for technical reasons to protect the rest of the recent flaps. This is to be closed after another few weeks. Rheumatoid activity all but ceased after closing the wounds, and adalimumab (Humira®) now having been given long enough to be effective. the patient is currently going through a rehabilitation program. He will most likely be placed on lifelong anticoagulation.

Case #2

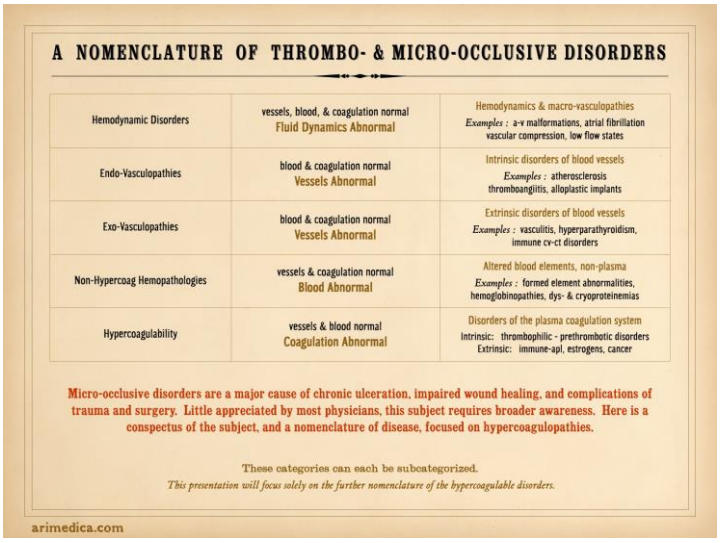
This is a 52 year old man, previously healthy, who presented with acute but otherwise ordinary diverticulitis of the colon requiring urgent surgery. He had the customary surgery required for the condition, but bowel resection was complicated by necrosis and leak of the anastomosis. Such complication is an inherent risk after bowel resection, but with each subsequent intervention, there were similar complications. Further procedures to debride or revise were all complicated by progressive thrombosis or infarction of bowel and abdominal wall. After a series of these events, further surgery was suspended. Topical care and nutritional support allowed the patient to recover but with wounds, hernia, and fistulas. A year later, seeming to be stable and non-acute, a new round of activities tried to fix the fistulas and close the wounds, resulting in more necrosis and bigger wounds or fistulas. Once again, surgery was suspended, and the patient was managed to allow stability. The resulting status is that the small bowel fistula is an exstrophied loop in the center of an open wound, making it difficult to apply a stoma appliance leading to leaks and dermatitis and impaired life style.

Two years after the initial presentation, a request was made for transfer and assumption of care. Once again, sight unseen, diagnosis was made of a primary hypercoagulable disorder, readily confirmed on acceptance of the patient and relevant workup. Highlights of the workup revealed very high fibrinogen along with high factor VIII and low protein S and antithrombin-3, all hypocoagulable species. Gene MTHFR was heterozygous positive, an inherent root of the hypercoagulable state. There were also high titers for anti-nuclear antibodies, dsDNA, and anti-chromatin, lupus indicators which, absent clinical signs, symptoms, and history of SLE represent a reflex autoimmunity due to the primary hypercoagulopathy. Hypothetically, inflammatory bowel disease could have caused his problems. IBD serologies were partly positive (anti-Saccharomyces), but gross and histological appearance of the bowel ruled out Crohn's disease.

Patient was started on wound care and intravenous heparin, which ran continuously including during surgery. After surgery, he was eventually transitioned to oral DTI apixaban. Despite two years of thrombo-infarctive complications of prior surgery, the surgery done after starting heparin was uncomplicated.

Goals of surgery were first and foremost to close the wounds and resurface the lower abdomen with normal skin that would accommodate effective use of a stoma bag. Repair of the bowel could be done if circumstances were perfect, but the realistic goal was to turn the fistula into a functioning defacto stoma, wounds, healed, then allow the tissues mature for 1-2 years, after which bowel restoration and abdominal wall reconstruction could be contemplated. (The fistula was distal along the small bowel, allowing it to be a manageable and nutritionally sound stoma.) Surgery was done using a hypogastric fasciocutaneous flap to restore skin to he lower abdomen. The fistula was "matured" through a cutout in the flap. There was never any errant ischemia or necrosis in the flaps or wounds (see picture caption below for details). All progressed as hoped for, and patient was eventually discharged with a secure sealed stoma bag draining a normal oral diet. Once the hypercoagulable diagnosis was confirmed and heparin started, there were no further coagulopathic complications or wound pathergy or necrosis.

Left top, image of the exstrophied small bowel and enterocutaneous fistula, and the surrounding wounds and dermatitis. **Left bottom**, start of the exposure during surgery, with blue ink showing pending lines of resection of old scar, to make room for the new flaps. The flap was a hypogastric fasciocutaneous flap based on the superficial inferior epigastric vessels. It turned 90° from its transverse donor orientation to lie vertical in the midline prepared wound. A circular cutout was then made through which the bowel fistula was brought to become the new stoma. **Right top**, completed surgery with stoma through hypogastric flap. **Right bottom**, at 8 days, there is no ischemia or necrosis except for a small area adjacent to the stoma. If this was an ordinary "bad flap", the distal part of the flap would be ischemic, but it is not. If the problem was from coagulopathy, then multiple edges of the incisions would have become ischemic, but that too is not the case. This problem resulted from perforating the flap and interrupting small vessels emanating from the flap pedicle. Once the patient was on heparin, there was never an errant speck of random ischemia, infarction, necrosis, or dehiscence.



3
A Nomenclature of Thrombo- & Micro-Occlusive Disorders

The 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. This presentation is a conspectus of the subject with the focus on the hypercoagulopathies. This panel presents a nomenclature of the micro-occlusive disorders of which the hypercoagulopathies are just one subset.

Recall what the function of thrombosis is – to stop bleeding from injured blood vessels. The plasma protein blood coagulation system, along with platelets, is tuned so that ideally the system is never activated when flowing blood is looking at normal endothelium, but it triggers and auto-amplifies quickly when the system "sees" any extra-vascular chemistry or histo-anatomy. All physicians have some familiarity with what happens when the system is untuned toward a hypocoagulable state, with hemorrhagic risks or events resulting from trauma, hemorrhage, sepsis, factor deficiencies, marrow suppression, anticoagulant drug effects, etc. Hypercoagulability remains largely misunderstood, unknown, or under appreciated, even though it is common and has a variety of significant clinical syndromes and sequelae. Hypercoagulable states have a wide spectrum of etiologies which can be primary (e.g. gene mutations) and secondary, including induced (e.g. auto-immune thrombogens) and reactive (e.g. anti-thrombin proteins). They also have a wide spectrum of clinical sequelae, syndromes, and presentations.

The quintessential fault in hypercoagulable states is that the blood coagulation system is over-tuned, likely to trigger and clot with normally sub-threshold stimuli, including spontaneous thrombosis within uninjured blood vessels, and overly aggressive thrombosis following injury. The clinical consequences may involve large vessels and organs and be acute and overt. They may involve small vessels and be subtle, occult, persistent, and hard to recognize or treat. Hypercoagulable states can be grouped among a broader category of disorders, the thrombo-occlusive and micro-occlusive disorders. These are a consequence of pathology or alterations in hemodynamics, blood vessels, the various other components of whole blood, and the plasma protein clotting system itself. Various combinations of these causes can occur, and vascular and hematological disorders superimposed on a background hypercoagulable state can be especially problematic. While the large vessel complications of hypercoagulability are themselves a major subject, with regard to chronic and pathological wounds our interest is in micro-thrombosis and micro-occlusion. The micro-thrombotic disorders can be grouped by a few major pathophysiological mechanisms:

1 – Hemodynamic disorders: Blood vessels, blood, and coagulation are all intrinsically normal. Thrombosis occurs from blood stasis due to hemodynamic alterations related to gross cardiovascular anatomy and function (e.g. atrial fibrillation, valvular pathology, a-v malformations, vascular compression, low flow states).

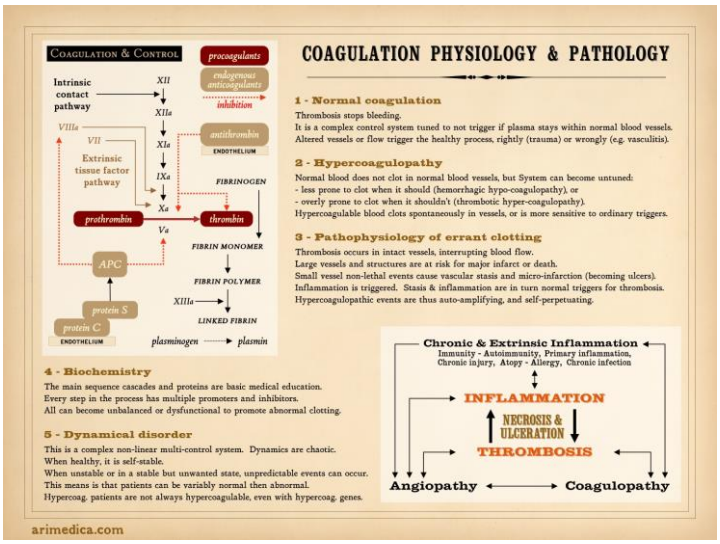
2 – Endovasculopathies: Intrinsic and luminal vasculopathies in which blood vessels are abnormal. Blood is normal, and coagulation is intrinsically normal. Thrombosis occurs in response to blood stasis or thrombotic activation created by endoluminal and endothelial alterations in the vessels. The causative disorders or defined pathologies are inherent or primary diseases or alterations of the blood vessels (e.g. atherosclerosis, other arteriosclerosis, thromboangiitis, alloplastic implants).

3 – Exovasculopathies: Extrinsic and mural vasculopathies in which blood vessels are abnormal. Blood is normal, and coagulation is intrinsically normal. Unlike endovasculopathies in which thrombosis is triggered by thrombogenic surfaces and flow turbulence or stasis on anatomically altered vessels, the exovasculopathies tend to be inflammatory or immune or metabolic in origin. Primary diseases extrinsic to vessels have effects on them, creating inflammation and thrombogenic mediators which trigger thrombosis in passing blood (e.g. venous vasculitis, lupus-scleroderma, other connective tissue disorders, classic arteritides such as polyarteritis nodosa and thromboangiitis obliterans, and hyperparathyroidism).

4 – Non-hypercoagulable hemopathologies: Micro-occlusive disorders in which vessels are normal and the plasma protein coagulation system is intrinsically normal, but other elements of the blood are abnormal. The clotting system responds "correctly" to abnormal conditions of stasis or thrombotic activation (1 - hemoglobinopathies, e.g. sickle, thalassemia, hemolytic anemias; 2 - dys- and cryoproteinemias, e.g. cryoglobulins, cryofibrinogen, macroglobulins, gammopathies & myeloma; 3 - formed element abnormalities (red cells, leukocytes, platelets, e.g. spherocytosis, myeloproliferative disorders, polycythemias, leukemias).

5 – Hypercoagulable hemopathologies: Vessels are normal. Blood is normal (formed elements and serum). What is abnormal is the plasma protein clotting system. In the above categories, the clotting system is behaving properly in response to abnormal conditions. In the hypercoagulopathies, abnormal inappropriate thrombosis is the primary event. Blood stasis and vascular occlusion are consequences, not causes. The hypercoagulable disorders can be intrinsic (the "thrombophilic" or "pre-thrombotic" primary disorders of the coagulation system) or extrinsic due to metabolic or auto-immune alterations (e.g., immune and anti-phospholipid antibody syndromes, estrogens and pregnancy, cancer).

Note that various primary disorders can have multiple effects that place them in two or more of the main categories. Each of these five categories can be subcategorized and subject to detailed discussion. This presentation will focus solely on the further nomenclature of the hypercoagulable disorders, and their clinical sequelae, diagnosis, and treatment.



4
Coagulation Physiology and Pathology

Coagulation is a complex system of a dozen main-sequence proteins, and many cofactors, modulators, promoters, and inhibitors, along with triggers that activate the system. 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.

From a physics or dynamical perspective, coagulation is a complex non-linear multicontrol system, which will be explained on subsequent panels. It is amazing that the thrombosis-coagulation system works so well, but it is also no surprise that the system will be prone to physiological and pathological variances, including baseline drifts, offsets, system re-tuning, and extrinsic perturbations 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. Key biological and functional considerations about the system are reviewed here :

4 – Biochemistry. The core physiology of thrombosis and plasma protein clotting is basic textbook science, and the process will not be detailed here. The panel summarizes the basics. There are two main "input channels" to trigger the system, Intrinsic Pathway which starts with activation of Factor.XII (Hageman) on seeing collagen. The Extrinsic Pathway starts when F.VII (proconvertin) binds to extravascular TF (tissue factor). Both pathways coalesce at the Common Pathway where F.V (proaccelerin) and F.X (Stuart–Prower) regulate conversion of F.II (prothrombin) to active thrombin which in turn amplifies the conversion of F.1 (fibrinogen) to the final fibrin gel. Degradation pathways exist to lyse fibrin. These many large proteins, including their primary amino acid sequences and also their secondary-tertiary geometries, provide ample opportunities for various chemicals to alter or interfere with the process, from diminishing factor production in the organs of origin, to amplification-acceleration or else inhibition of the zymogen conversions, to interference with the binding sites and biological activities of each of these species. Promoters and inhibitors can be physiological, pathological, or exogenous, and they can serve the life-saving greater good of the host or lead to nefarious complications. Complications result when the system becomes unbalanced such that blood is hypocoagulable and cannot stop bleeding , or else becomes hypercoagulable and clots within flowing blood vessels.

1 - Normal coagulation. The purpose of the plasma proteins and thrombosis is to stop bleeding. It is a complex control system that is ordinarily tuned or balanced such that it will not trigger if plasma stays within normal blood vessels. But, its purpose and its normal tuning are such that it will activate upon provocation. The provocations include altered environment (injured or disordered vessels, or inflammation) or alterations in blood flow (with stasis or turbulence). Intent of the system is to trigger and make clot upon seeing anything that is not normal vascular endothelium.

When the healthy plasma protein coagulation system does trigger, it is usually correct, due to trauma and injured blood vessels, thereby stopping bleeding. But, it can be errant, wrongly clotting for conditions such as vasculitis, vascular implants, or flow alterations as in atrial fibrillation.

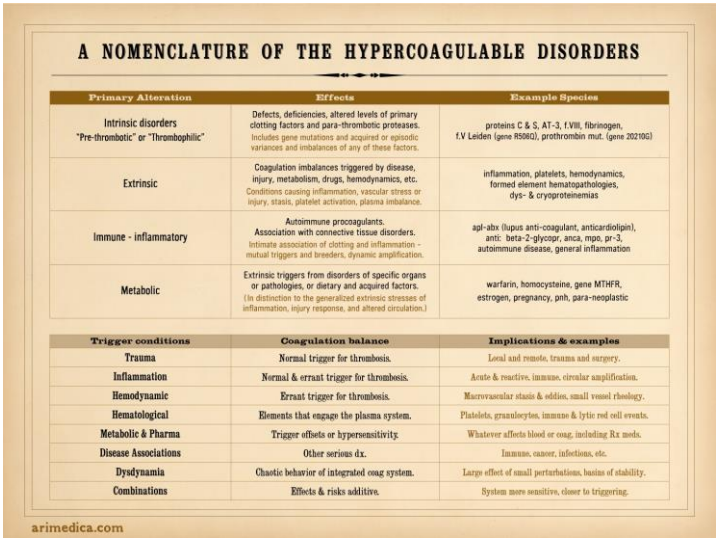
2 – Hypercoagulopathy. Normal blood does not clot in normal blood vessels, but this system can become untuned. It can become (1) less prone to clot when it should (hemorrhagic hypo-coagulopathy), or it can become (2) overly prone to clot when it shouldn't (thrombotic hyper-coagulopathy). Hypercoagulable blood clots spontaneously in vessels, or it is more sensitive to ordinary triggers. Errant intravascular thrombosis interrupts blood flow to tissues and organs causing tissue ischemia and possible infarction, which in turn causes a variety of secondary effects of lesser or greater or even fatal consequence.

3 – Pathophysiology of errant clotting. In the hyper-thrombotic hyper-coagulopathies, thrombosis occurs within 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. Micro or focal infarcts can become skin ulcers or a variety of other clinical disorders. However, the pathogenesis of the hypercoagulable disorders reaches beyond just vascular interruption and ischemia. Thrombosis is a potent initiator of inflammation. As a normal response to normal protective thrombosis, that is proper and healthy. However, errant and repetitive microthrombosis and microinfarction cause persistent acute inflammation. Inflammation in turn is a potent initiator of thrombosis. In states of persistent thrombosis and inflammation, the system tends to auto-amplify this errant state, making the problems progressively worse and self-perpetuating. Note only does this risk ever greater likelihood of wound pathergy and complications of the disease or of trauma and surgery, but this is a breeder state that can lead to auto-immunization and the onset of collagen-vascular connective tissue disorders (discussed on pending panels).

5 – Dynamical disorder. The coagulation system is a complex non-linear multi-control system. This means that the system dynamics are chaotic. This is all explained on a pending panel. There are some predictable and clinically relevant implications of this. The system is self-stable, and when it is healthy, it tends to stay that way, properly tuned to clot for bleeding but not clot otherwise. When the system drifts into a self-stable but clinically adverse state, it tends to stay there as well. When the system is unstable, unpredictable behaviors are the rule. This also means that patients can be variably normal then abnormal. In other words, patients with actual or latent hypercoagulable disorders are not always in a hypercoagulable state, even those with hypercoagulable genes.

Inflammation-Thrombosis. Thrombosis is a complex non-linear multicontrol system. Its feedback interactions with inflammation are another degree of non-linearity and chaos that can complexify its dynamics. These concepts are at the heart of why, in the natural state of given patient, coagulation can misbehave or be sensitive to conditions or locked into undesirable adverse behaviors. This non-linearity or complexity also explains the persistence of chronic wounds in the face of these disorders, and the breeder effects leading to auto-immunity. At the heart of these pathophysiological states is the co-dependent interplay between thrombosis and inflammation.

Recall the quintessential functions of inflammation and thrombosis. When an injury occurs, how is it recognized? How is it cleaned up? How is the repair process started? Platelets and thrombosis are one pathway of injury recognition. Aside from their blood clotting roles, once triggered, they also initiate inflammation so the body can handle defenses, do damage control, and then clean up. Thus, (1) thrombosis triggers inflammation. However, inflammation also creates a milieu that promotes thrombosis via prothrombotic chemicals, leukocyte and platelet trapping, changes in vessels and blood viscosity, etc. Thus, (2) inflammation triggers thrombosis. They trigger each other. This complex non-linear system is self-amplifying. In the case of single incidental injury, such as mechanical trauma, this thrombosis-inflammation coupling ensures a swift ramp up of defensive changes, but then the process subsides and settles, paving the way for repair. In simple terms, trauma induced thrombosis-inflammation is a one-shot. However, when there is repetitive or sustained injury, then new thrombosis and inflammation keep getting triggered, keeping the process alive or renewed. What conditions can create such a state of repetitive or sustained injury? These can be (1) chronic or repetitive trauma, (2) thrombosis-inflammation triggered by hypercoagulable or micro-occlusive disorders, and (3) acute inflammation repeatedly induced by immunity, allergy, or infection. While the nature of thrombosis and inflammation is to protect the host from injury and invasion, when they are sustained by these repetitive stresses, then the interactive pathology becomes perpetuated, self-sustaining, and locked in, usually to the detriment of the host.



A NOMENCLATURE OF THE HYPERCOAGULABLE DISORDERS

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

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

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5
A Nomenclature of the Hypercoagulable Disorders

Hypercoagulable disorders and states reflect a variety of pathogenetic mechanisms. Due to the complexity of the plasma coagulation system, there are various elements of it or external perturbators that can vary in ways which increase the tendency to clot. Among the many stresses or mechanisms, certain categories or commonalities can be seen. Primary alterations can be grouped into four categories, each having certain effects and associated dynamics or chemical species.

1 – Intrinsic disorders, "pre-thrombotic" or "thrombophilic". These are defects, deficiencies, or altered levels of primary clotting factors and para-thrombotic proteases. Includes gene mutations and acquired or episodic variances and imbalances of any of these factors. Typical species for which there is a standard clinical lab test include proteins C & S, AT-3, f.VIII, fibrinogen, f.V Leiden gene (R506Q), and prothrombin gene mutation (20210G).

2 – Extrinsic disorders. Coagulation imbalances triggered by disease, injury, metabolism, drugs, hemodynamics, etc., i.e. conditions extrinsic to the core plasma protein system which bear upon that system. These are a

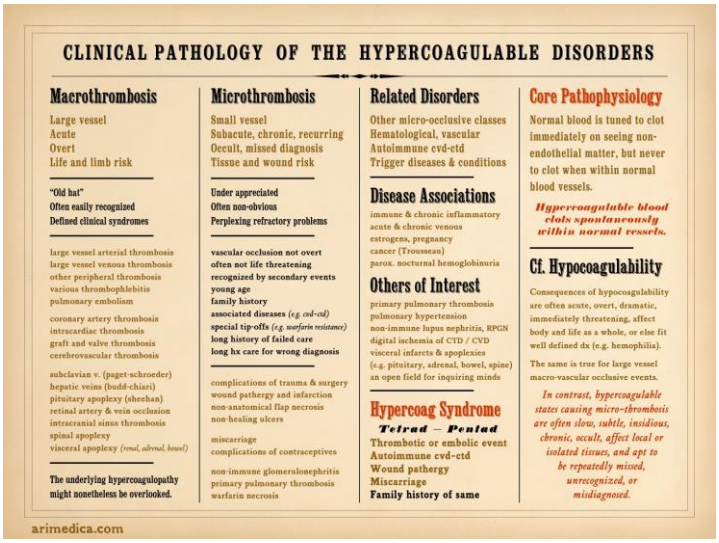
multitude of conditions causing pro-thrombotic stresses, including inflammation, vascular injury, stasis, other altered hemodynamics, formed element hematopathologies, platelet activation, plasma imbalance, and dys- & cryoproteinemias

3 - Immune – inflammatory. This encompasses a group of immune procoagulants which arise in conjunction with some type of auto-immunity. Hypercoagulable patients in this category are likely to have some set of signs and symptoms revealing an autoimmune disorder, most frequently the classic connective tissue disorders or collagen vascular diseases (cvd-ctd), but any autoimmunity is at risk (e.g. inflammatory bowel disease, multiple sclerosis, pemphigus or psoriasis, gammopathies). The intimate association of clotting and inflammation is central to this category. The inter-operations of these two dynamics leads to mutual triggering and amplification. These are breeder conditions for each other, with chronic immune mediated inflammation upregulating prothrombotic chemical species, and primary hypercoagulability causing the auto-immune recognition that spawns the cvd-ctd's. These disorders encompass the antiphospholipid antibody syndromes and other unspecified clinical profiles. For wounds, these are the most refractory to ordinary care, good results coming only from a combination of anticoagulants, plus steroids or other anti-immune therapies, plus plasma pheresis / plasma exchange for some. Typical species for which there is a standard clinical lab test include lupus anticoagulant, anticardiolipins, b2g (anti-beta-2-glycoprotein), anca's (anti-neutrophil cytoplasmic antibody), mpo (anti-myeloperoxidase), & pr3 (anti-proteinase-3). These immune procoagulants are active against various species of the plasma coagulation system (lupus anticoagulant versus thrombin, anticardiolipins versus Protein S).

4 – Metabolic disorders can affect coagulation. These are stresses extrinsic to the coagulation system, often exogenous to the host, resulting from specific disorders of other organs or metabolic systems, including acquired factors such as dietary and pharmaceutical. (These focal metabolic stresses are in distinction to the generalized extrinsic stresses of inflammation, injury response, and altered circulation.) Conditions and causes include warfarin necrosis, homocysteine, gene MTHFR, estrogens, pregnancy, pnh (paroxysmal nocturnal hemoglobinuria), and para-neoplastic syndromes.

In addition to these four general categories of hypercoagulable causes and disorders, remember that these are often just sensitizers. They readjust the tune or balance of the clotting system, giving it an "itchier trigger finger", making it more likely to activate with a smaller provocation. These conditions lurk in the background, often unbeknownst to patient or physician, until some trigger comes along. The triggers include the following. Some of these are obvious. Others my be unintuitive or unfamiliar, such as dysdynamia and chaos, but they will be discussed in later panels:

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 non-hematological diseases	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



6
Clinical Pathology of the Hypercoagulable Disorders

This and the following few panels discuss clinico-pathological features of the hypercoagulable disorders. The following ones focus on their clinical behaviors, findings, and diagnosis of these conditions. This panel focuses on relevant anatomy, physiology, and pathology. In considering the clinicals about these disorders, two important comparisons must be made, the difference between hyper- and hypo- coagulable states, and the distinction between large vessel macrovascular thrombosis versus small vessel and microthrombosis.

Core Pathophysiology
Normal blood is tuned to clot immediately on seeing non-endothelial matter, but never to clot when within normal blood vessels. But the blood clotting system can become untuned or unbalanced. When blood or the thrombosis system is ***hypocoagulable***, it fails to clot, thus fails to perform its primary function of stopping bleeding. When they are ***hypercoagulable***, blood clots spontaneously within normal vessels.

Clinicians are generally quite familiar with the hypocoagulable states, when active bleeding will not stop. They often fit common or well defined clinical conditions such as sepsis, trauma, transfusion coagulopathy, hypothermia, liver failure, hemophilia, and over-anticoagulation. The consequences of hypocoagulability are often acute, overt, dramatic, and affect body and life as a whole. They can be immediately threatening to the host and anxiety provoking for the physician who must implement an urgent correction.

These comments mirror the urgent situations that occur with occlusion of large blood vessels. When vessels are blocked, blood fails to flow and affected ischemic organs risk infarction. Macrovascular occlusion has various causes including trauma, compartment and compression syndromes, endovasculopathies such as atherosclerosis, and hypercoagulable states. Since the current topic is hypercoagulability, we can disregard the other causes and focus solely on hypercoagulable disorders causing errant or spontaneous thrombosis. When large vessels clot, we recognize the condition because of acute ischemia that affects large organs and tissues. In fact, the events can be impossible to overlook or ignore, such as

strokes (cva), heart attacks (mi), acute venous phlegmasia (dvt), shortness of breath from pulmonary embolism (pe), or acute thromboembolic gangrene of an extremity. To quote the preceding paragraph. *"The consequences of ~~hypocoagulability~~ MACROVASCULAR THROMBOSIS are often acute, overt, dramatic, and affect body and life as a whole. They can be immediately threatening to the host and anxiety provoking for the physician who must implement an urgent correction."*

The hypercoagulable disorders can and do cause overt large vessel thrombotic events. However, far more common is that they cause small vessel or microthrombosis. In contrast to the drama of hypocoagulable bleeding and large vessel thrombosis, the clinical consequences, syndromes, and scenarios resulting from hypercoagulable states tend to be slow, subtle, insidious, chronic, and occult, affecting local or isolated tissues, and apt to be repeatedly misdiagnosed or missed altogether. Failure to appreciate that these disorders exist, and failure to appreciate the spectrum of clinical presentations is as pernicious as the disease itself when it results in overlooked diagnoses and irrelevant or ineffective care for wrong diagnoses.

Macrothrombosis. Thrombosis and obstruction at a macroscopic level affects large vessels which generally supply whole organs or large body segments. Acute infarction of the affected organs or disruption of their functions is not tolerated, so recognition of the event is acute and overt. Risks to life and limb are substantial. These are "old hat" or "old medicine" syndromes, items which, precisely because they are easily recognized, have been pondered and described, diagnosed and treated by physicians for centuries or millenia. They tend to be defined clinical syndromes, often eponymous, inscribed in introductory textbooks, taught to medical students, and generally recognized by most physicians. A non-comprehensive listing includes conditions such as these:

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 vein thrombosis (Paget-Schroeder), hepatic veins (Budd-Chiari), pituitary (Sheehan), retinal artery & vein occlusion, intracranial sinus thrombosis, spinal apoplexy, visceral apoplexy (renal, adrenal, bowel), thrombotic priapism, childhood thrombosis.

Oftentimes, these disorders are consequent to other or underlying pathologies or conditions which themselves are easy to diagnose. For instance, atrial fibrillation can cause mural thrombus. Postural dependency of the lower extremities can cause deep venous thrombosis. Dvt of the lower extremities can cause chronic venous stasis ulceration. Dvt of the lower extremities can cause pulmonary embolism. Atherosclerosis of peripheral arteries can cause extremity thrombosis and gangrene. Valvular heart disease can cause extremity thromboembolism and gangrene. Bleeding, hypotension, or shock can cause infarction of the adrenals or pituitary. Heart bypass surgery or aortic exclusion can cause spinal cord infarction. Initiation of oral therapy with estrogens can cause hepatic thrombosis or with warfarin can cause skin necrosis. The question to be asked is why are some patients victimized by the dangerous sequelae of these events, whereas others have no problems? Why do most people have heart surgery without consequence but some become paraplegic? Why do most people have free flaps for reconstructive surgery without consequence, but some lose their flaps despite technically perfect anastomoses? Why do most women who start birth control hormones have no complications, but some get Budd-Chiari? Why do many people have dvt's with no consequence, but some get chronic stasis ulcers? Why are thrombotic and embolic events unusual in children yet sometimes occur without other overt cause?

If you remain unaware that there is a large category of illness called the hypercoagulable disorders, then you will fail to realize that many of these patients had a reason to have a thrombotic or infarctive complication of the primary condition. The thrombotic complication was not just a random statistical event because "5% of people with Abc condition get Xyz complication, and sorry, you are just one of those statistics". When an adverse secondary thrombotic or infarctive events occurs in response to another primary condition, especially one well known to be associated with thrombotic complications, then there is a high likelihood that that patient has a hypercoagulable disorder. Even though the macrothrombotic conditions are "old school" syndromes, it is incumbent on the modern physician to adjust your understanding of them to appreciate that they likely occurred because of an underlying unrecognized hypercoagulopathy. That is the nature of these disorders. They do not always make spontaneous clots for no reason. They reset the threshold or trigger point for thrombotic activation, and then when another potentially clot inducing event occurs, it is more likely that a clot will actually form.

Never be content to diagnose solely the main macrovascular event. The organ infarcted because of a clot, and there is a reason that the clot occurred. There could be miscellaneous identifiable and mundane reasons, but never fail to consider that a hypercoagulable disorder is responsible. Do not overlook these diagnoses.

Microthrombosis. Unlike the overt drama of hypocoagulable states and macrothrombotic events, hypercoagulable states and microthrombotic events affecting small vessels are subacute and chronic. They are slow, subtle, persistent, recurring, perplexing, frustrating, and refractory to diagnosis and treatment. Even the vascular occlusion per se, being at a microscopic level, is not overt. The clinical presentation for a particular patient might be straightforward, e.g. a dehisced wound, a thrombosed graft, a chronic leg ulcer, a repetitive miscarriage, the 20th pulmonary embolism. However, the cause of that macro event might be elusive and non-obvious in origin, the vascular occlusion not overt, unless you are familiar with the spectrum of micro-occlusive disorders and they clinical events they cause. Unlike the macrothrombotic events which are immediately life and limb threatening, the micro-occlusive events often put tissues and wounds at risk but not the whole person.

Some clinical events ought to raise immediate "red flags" of a possible underlying hypercoagulable disorder: recurrent miscarriage, dvt, or pulmonary embolism; a leg ulcer with a pure thrombo-infarctive pattern of injury; a lupus patient whose surgical incision infarcts; a seemingly normal patient whose surgical incision infarcts; skin necrosis after starting warfarin, or liver failure and ascites after starting birth control pills. There are other conditions which are not common to begin with, and thus even less likely to make the correct association with hypercoagulability, e.g., rpgn (rapidly progressive glomerulonephr-"itis") and other non-immune glomerulonephritis, primary and multi-focal pulmonary thrombosis, spinal infarction after surgery or trauma. Failure to appreciate the cause and connection misses the true underlying diagnosis and puts the patient at risk for more of the same and progressive deterioration. This situation is central in the histories of many such patients – a long series of recurring morbid events, progressive complications and disabilities, refractory and perplexing resistance to treatment, and multiple failed care. Remember, wrong diagnosis, wrong treatment. Failure to recognize these disorders means that the correct therapy is not instituted, so no improvements are made. All too often the story is worse than that, as when surgery or trauma cause wound pathergy and tissue necrosis, prompting more surgery

which cause more necrosis, leading to a deteriorating cycle of increasing morbidity and tissue loss. Sadly, all of this misery can be arrested by starting anticoagulants, but if the true diagnosis is not recognized, then the effective treatments not started. That is the terrible story of the two patients presented as the index cases at the beginning of this presentation.

The hypercoagulable disorders and hypercoagulable states do not speak for themselves. They cause secondary complications which bring the patient to attention. It is the doctor's job to sniff out the underlying real problem. Fortunately, these disorders can be diagnosed on positive criteria. This is detailed on subsequent panels, but it is worth noting now that patients will generally provide many clues or tipoffs that a hypercoagulopathy is present. These insights include:

§ Problems occur at any age including youth; family history is often strong for similar or other thrombotic events; there are strongly associated conditions such venous stasis or the cvd-ctd's; patients typically have a long history of failed care or care for the wrong diagnosis.

§ Unexpected, inexplicable, or recurrent complications of trauma & surgery; wound pathergy and tissue infarction; necrosis of flaps in non-anatomical or non-rheological patterns; chronic non-healing ulcers.

§ Multiple idiopathic miscarriages; family history of miscarriage; complications of hormonal contraceptives.

§ Odd and irregular thrombotic events, e.g. myocardial infarction in a young person, a family history of youthful heart attack, or coronary thrombosis absent atherosclerosis.

§ Recurring thrombotic events despite nominally adequate anticoagulation; recurring pulmonary "emboli" despite filters or venous interruption; difficulty regulating warfarin or other anticoagulants; distinctive or contrary responses to treatment such as profound or erratic warfarin resistance or else warfarin necrosis.

§ Atypical diseases inconsistent with generic diagnosis or unresponsive to generic treatment, e.g., non-immune glomerulonephritis, primary pulmonary thrombosis; non-neuropathic otherwise idiopathic chronic pain and fatigue syndromes.

Hypercoagulable disorders can cause both macro- and micro-thrombotic events and complications. Keep in mind that the macroscopic vascular occlusions and infarcts can occur for a variety of reasons. Most coronary, carotid or cerebral, or femoropopliteal thromboses occur because of the thrombogenic effects of atheromas. Such a patient could coincidentally have a hypercoagulable disorder which will make the risk of acute thrombosis higher, but there is no need to implicate hypercoagulability with every mundane vascular event. On the other hand, the odd, infrequent, and non-endovasculopathic thromboses in young and healthy patients, such as Budd-Chiari and Paget-Schroeder should always be considered for coagulopathic workup. Always remember that the odd macrovascular events do not happen just "because". Look for the hypercoagulable disorder. In contrast, the microthrombotic events are usually occult. So, be aware of their spectrum of presentation, and when you see the derivative events, work the patient up for the thrombotic disorders.

Related disorders and disease associations. In addition to the face value thrombotic nature of these disorders, they are often associated with or accompanied by other distinctive disorders. First, the superset of the hypercoagulable disorders are the micro-occlusive disorders. Thus, a patient whose clinical profile fits perfectly with hypercoagulability might actually have normal plasma and intrinsic clotting, but instead has another hematopathology such as sickle, thalassemia, or spherocytosis, or else thrombocytosis or myeloproliferative disorder, or a cryo-proteinemia or gammopathy. The problem might instead be with thrombogenic blood vessels, such as micro-atherosclerosis, secondary or tertiary hyperparathyroidism, autoimmune vasculitides such as thromboangiitis obliterans (Buerger's), or other autoimmune angiopathies (lupus-scleroderma). Because of the strong interplay between thrombosis and inflammation, they become mutual breeders for intrinsified hypercoagulability or stromal auto-immunity. Patient with hypercoagulability frequently have strong makers of auto-immunity, and vice versa, so always consider the connection of the HCD's (hypercoagulable disorders) to the CVD-CTD's. Also, these disorders have an interplay at the moment of thrombosis, as when antiphospholipid positive hypercoagulable blood flows at low velocities or dwells too long in vessels affected by scleroderma angiopathy, or when thrombophilic Factor V Leiden affected blood flows past the inflamed and restricted vessels of leukocytoclastic vasculitis. Finally, always consider the wide spectrum of trigger conditions that can push "sticky" hypercoagulable blood to the threshold where the thrombotic cascade suddenly "turns on" and auto-amplifies.

The connection between chronic inflammatory, autoimmune, and hypercoagulable disorders bears repeating. The collagen-vascular connective tissue disorders are bred by some other chronic underlying disorder of repetitive injury, allergy, infection, inflammation, or thrombosis. The pathogenetic mechanism will not be reviewed in this presentation. Suffice to emphasize that hypercoagulable and auto-immune disorders are frequently connected, both present in the same subject, immutable evidence of both such as positive prothrombin gene mutation in conjunction with overt crippling rheumatoid arthritis, or recurring wound pathergy or venous thromboembolism in a patient with high anti-cardiolipins and active lupus including nephritis, arthritis, sicca, and cerebritis.

Another strong correlation with hypercoagulability is chronic venous disease. Many patients who are not hypercoagulable have had venous thrombosis for reasons of venous hypertension, postural stasis, or trauma. They might get varicose veins, or they might get chronic "milk leg" phlegmasia alba, but that does imply that they will get chronic "venous disease" with its chronic progressive venous vasculitis, inflammatory panniculitis and dermatitis with liposclerosis, and refractory ulceration. As a purely hemodynamic disorder, venous reflux and hypertension have been understood since circa 1800, but what is missing in that appreciation is why some people get inflammatory venous disease and others do not. Why did some of them get thrombosis and damaged valves in the first place? Why are some of their wounds easy to heal, but others are perennially refractory to care? Venous disease itself is not a certainty that a hypercoagulable disorder is present, but many people with venous disease and ulcers do indeed have factor V Leiden or other hypercoagulable species. When hypercoagulability is present, it is a "two-edged sword" of pathology. It causes the overt or occult venous thrombi that cause valvular incompetence and the post-phlebitic state, and then when liposclerosis and ulceration eventually ensue, the hypercoagulability also impairs healing. Consider the possibility of hypercoagulability and the need for anticoagulation in venous patients who have been refractory to care or have progressive ulceration, or have wound biopsies with distinctive microthrombosis, and especially if their leg problems or antecedent dvt's occurred in childhood.

Other highly correlated disease associations include estrogen use, pregnancy, cancer and para-neoplastic syndromes (e.g. Trousseau syndrome), paroxysmal nocturnal hemoglobinuria, and nutritional and metabolic disorders that affect homocysteine. As with immune and venous problems, the connection to hypercoagulability is not always present, perhaps even infrequent. Obstetrical complications and cancer sequelae are usually due to

something else. "Patient has cancer, therefore think about a hypercoagulable disorder" is an incorrect proposition. However, the converse is true, "patient has had a thrombo-infarctive event in the face of cancer, so do a hypercoagulability workup", or " patient has had a thrombo-infarctive event plus other telltale signs and symptoms, so consider underlying cancer and do the workup." Do not make a false diagnosis of hypercoagulability if it is not there, but that mistake is rare. All too often the reverse is true, that the hypercoagulable diagnosis is there and real but overlooked and left untreated.

Finally, there are disorders that are most likely due to hypercoagulability, evidence abounds, and for individual patients the association is incontrovertible. For some of these conditions, the connection is established, just not widely appreciated. For others, the connection is empirically sound but relevant large studies have not appeared that confirm the association, establish a relative incidence, or clarify how to discriminate the coagulopathic versions of these disorders from the non-coagulopathic versions. Such disorders include:
- Primary pulmonary thrombosis, in which thrombi occur in the lung, not embolization from peripheral veins. Primary intrapulmonary thrombosis has long been documented from post-mortem pathological studies, and in living subjects it can be inferred from angiography, from the multi-focal distribution, and from the persistence or irrelevance after use of filters. The concept is now more widely appreciated, often designated as PPT (primary pulmonary thrombosis) or ISPAT (in situ pulmonary artery thrombosis).
- Pulmonary hypertension has various etiologies, but one of them is chronic recurring occlusion of small pulmonary vessels from either PPT / ISPAT or else recurring embolic occlusion coming form the periphery, CTEPH (chronic thrombo-embolic pulmonary hypertension).
- Non-immune lupus nephritis and RPGN (rapidly progressive glomerulonephritis). These are glomerulonephropathies in which the autoimmune connection might be there in a patient with lupus or other cvd-ctd, but there are no glomerular immune crescents histologically. In RPGN, there maybe no immune component at all, not even any acute inflammation, invalidating the "-itis" designation, just failing glomeruli with histological presence of fibrin thrombi in the glomerular capillaries.
- Digital ischemia of CTD / CVD, especially in lupus and scleroderma and Raynaud's. Raynaud's phenomenon and vasospasticity do not infarct fingers or cause ulcers. These later complications are categorically associated with the distinctive lupus-scleroderma acral fibromuscular angiopathy, and infarcts are more likely in those with concomitant hypercoagulability.
- Visceral infarcts & apoplexies, e.g. pituitary, adrenal, bowel, spine. Given that these tend to occur during odd and unusual circumstances, often in young or seemingly heathy people, always keep an open mind that when they do occur, there is an underlying hypercoagulable state.
§ This is an open field for inquiring minds to correlate classic but poorly understood diseases with more robust modern understandings of occult diseases and complex pathogenesis.

The Hypercoagulable Syndrome
When approaching a patient in whom various features of history and exam suggest a hypercoagulable state, there is a simple and effective way to do a reliable screening that will guide whether the idea is genuinely likely or not, or if you should invest in an expensive laboratory workup for the hypercoagulable disorders. The Hypercoagulable Syndrome is a Tetrad – Pentad, having four intrinsic features plus the importance of family history. If these features are committed to memory and asked of each patient for whom you have a relevant concern, you will be able to get to the diagnosis, or rule it out, quite handily:

1 - Thrombotic or embolic event. A history of prior thrombotic event or thromboembolism. This could be a dvt or pe, blindness from retinal vessel occlusion, myocardial infarction at a young age or absent coronary artery disease, or any of the other macro-thrombotic events listed above.

2 - Cvd-ctd or other autoimmune disorder. The connection between these two domains has been emphasized, and is emphasized again. Patients might have an established diagnosis, already working with a Rheumatologist, or they might have signs and symptoms, overt or subtle, that have not yet had proper evaluation or diagnosis. Do not accept a simple answer of "no" when asking if a patient has rheumatoid or lupus. Do a relevant quick review of symptoms, asking about arthralgias, morning stiffness, sicca, rashes, sun sensitivity, multiple allergies, ocular symptoms, urethral symptoms, etc. Also, do not accept prior diseases at face value. A patient who has had refractory "seizures" unresponsive to all anti-epileptic drugs may not have seizures at all, rather lupus cerebritis. A patient with "Raynaud's" that has finger ulcers or infarcts no longer has Raynaud's, rather a more advanced state of anatomical angiopathy quite possibly with hypercoagulability. A patient with refractory IBS irritable bowel syndrome might instead have IBD inflammatory bowel disease. Remember, you are seeing the patient for some particular reason, and the possibility of hypercoagulability has now come through, so ipso facto immune disorders have to be considered, and you now have greater insight into the patient's condition than the prior doctors, so do not be shy about trying to prove or disprove these diagnoses.

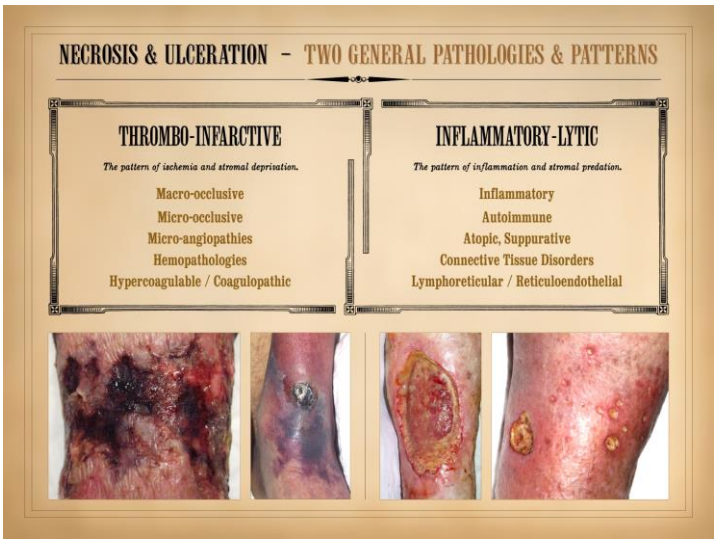
3 - Wound pathergy. This is any unanticipated, unexpected, or exaggerated complication of trauma, surgery, or wounds, especially wound infarction, dehiscence, flap necrosis, amputation, marginal ulceration, exaggerated non-suppurative inflammation, exaggerated pain, or any of these things after trivial injury such as nothing more than a needle stick. As surgeons, this is the most likely reason you will be seeing the patient in the first place. Indeed, the complication may have occurred during your care, and this part of the tetrad is thus automatic in your evaluation.

4 – Miscarriage. As with everything else on this list, there are many causes of obstetrical miscarriage. When fetal, placental, and other disorders have been ruled out, and the patient simply has a history of idiopathic miscarriage, especially if multiple times, then hypercoagulability is likely.

5 - Family history of same. Oftentimes a hypercoagulable patient will score low on the tetrad, but the family history is strong. Men of course cannot give a history of miscarriage, and some women have not, but if the sister, mom, aunt, and grandmother have all had it, it is the same as if the patient had it. A patient may deny an autoimmune disorder, but "my uncle had rheumatoid" or "my brother has lupus". That is a positive correlation. The same family history will be revealed for thromboembolic events, and likewise for things like chronic leg ulcers.

Having just one positive item, for example the wound that you are seeing, does not make the case. This is true likewise if the score is negative except for the incidental dvt that the vascular surgeon is seeing or the pulmonary embolism that the pulmonary doctor is seeing or the one time miscarriage that the obstetrician is seeing. Two positive items is suggestive of a hypercoagulable disorder, and laboratory workup will more likely than not reveal a positive or diagnostic value. Three positive items is nearly certain. Four positive items can be considered definitive. Five positive items are impressive. The stronger this history is, the more weight you have for doing a confirmatory lab workup, and the more weight you have for

starting anticoagulants and other relevant treatment even in the absence of laboratory confirmation. Recall too that we have only about a dozen or two lab tests for a system that has many dozens of places where the system can go wrong, so laboratory confirmation is not always successful. When the clinical syndrome is strongly positive, often with three positive items, and unequivocally with four or five items, then the diagnosis can be considered as established and treatment started.



7
The Clinico-Pathological Patterns of Ulceration

In discussing the effects of hypercoagulability on trauma, wounds, and surgery, the universal implication is for pathergy, infarction, and wound failure. When discussing wounds and tissue complications, there are two main words that describe the active onset and evolution of a wound, "necrosis" and "ulceration". These are the processes by which previously alive or present tissues die and disappear. There are various disorders that cause or influence the evolution of a wound or ulcer, but they all lead to just two common patterns and final pathways to necrosis and ulceration – the thrombo-infarctive pattern and the inflammatory-lytic pattern.

(1) Thrombo-infarctive necrosis and ulceration is a consequence of severe ischemia due to loss of blood flow. Obstructed circulation of any cause can be responsible. Large vessel macro-thrombosis with large organ infarcts or limb gangrene is one version of this which clinically is usually overt and obvious. With regard to non-life threatening pathological ulceration, CAP wounds ("Chronic And Pathological"), and the complications of trauma and surgery, the primary problem is usually obstruction of micro-vessels, causing small scale ischemia and infarction. This results from the various micro-occlusive disorders, including micro-angiopathies, formed element hematopathologies, and hypercoagulopathies and dysproteinemias. Clinically, the pattern is one of dry gangrenous infarction, including dry eschar, cyanotic vascular stasis or else pallor, and absence of edema and gross inflammatory changes. Laboratory measures of perfusion, such as TcpO2, laser doppler, and multi-spectral imaging are likely to show impairments. The underlying cause might not always be obvious, the patient might not have an overt or established history of a causative disorder, and the clinical presentation might not be dramatic or life and limb threatening. However, the physical findings are distinctive, which is enough to direct the clinician to focus on the occlusive disorders as main items on the differential diagnosis.

(2) Inflammatory-lytic necrosis and ulceration is due to active inflammatory states, including primary neutrophilic inflammation, atopic-allergic inflammation, and immune-lymphocytic inflammation, all resulting from various underlying diseases including the autoimmunopathies, collagen-vascular connective tissue disorders, and lymphoreticular diseases. Immunoglobulins, complement, and matrix proteases are abundant along with other acute inflammatory and chronic immune chemistry. Clinically, these are ulcers or tissue complications which have overt acute inflammation, including edema and scarlet red erythema. Rather than having dry infarcts and eschar, these ulcers simply erode, getting larger by the literal dissolution of the tissue by cell killing, complement-antibody and other cytolytic events, and protease and other destructive effects.

There is a third major category of tissue loss, trauma, which includes simple mechanical or surgical injury along with pressure, radiation, burns, toxic chemicals, etc. What discriminates trauma as a cause of a wound is that trauma is incidental and self-limited, whereas thrombo-infarctive and inflammatory-lytic ulceration are generally persistent and long-lasting due to active ongoing disease (and mutual sustentation when both patterns and pathologies are present). Angiocytes and fibroblasts are the two constituent cells of the generic stroma and wound healing process. Further discussion of this point is beyond the scope of this presentation, but these two cells are robust, with extraordinarily few intrinsic diseases and pathologies. They can be obliterated by trauma, by critical deprivation of blood supply, and by killers such as antibodies, leukocytes, and lymphocytes. Aside from the trauma causes of wounds, thrombo-infarctive and inflammatory-lytic ulceration and necrosis are the two – and the only two – common pathophysiological mechanisms by which the basic stroma of the body can be killed and degenerated.

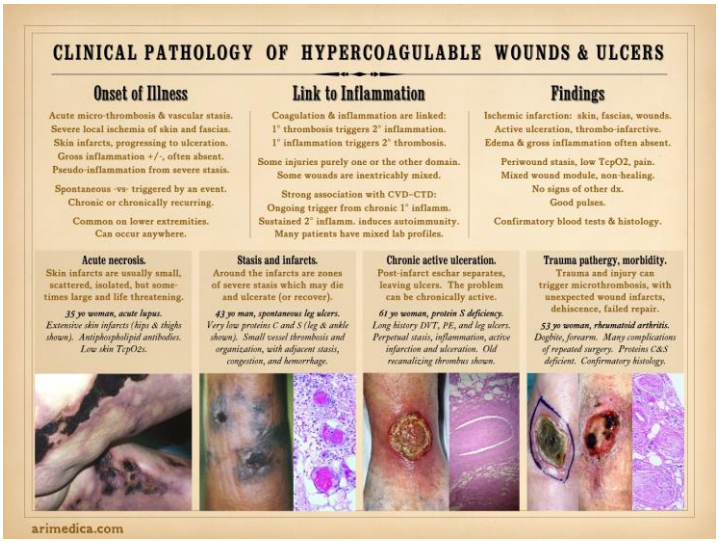
Many CAP ulcers and tissue complications are obviously of one origin or the other, predominantly thrombo-occlusive versus inflammatory-lytic. They can thus be easily discriminated by simple physical exam as to which underlying pathology predominates. However, because of the intimate and intricate inter-dependence of inflammation and thrombosis, and of the thrombotic and immune disorders, many ulcers will have features of both patterns.

Far left, this is spontaneous infarction and ulceration of distal leg skin in a woman with normal pulses who, on workup, was found to have antithrombin-3 deficiency. The infarcted skin is still there as dry black eschar. Viable tissues are free of notable edema or erythema. Also, the viable tissues are wrinkled, indicating not just absence of edema but active dehydration as inadequate blood flow fails to maintain normal tissue turgor. This is the pure thrombo-infarctive pattern of necrosis and ulceration. **Center left**, this is an ankle ulcer and infarct in a patient with diabetes and severe distal atherosclerosis. Emanating from the original ulcer is a progressive zone of sever cyanotic vascular stasis. The established ulcer has dry black eschar. Erythema, edema, and other inflammatory changes are absent from this cold extremity. Without sufficient circulation, not only will skin and necrosis have this pure thrombo-infarctive pattern, but inflammation cannot develop due to the limited blood flow. **Center right**, a leg ulcer in a patient with auto-immune lupus like symptoms (although no specific established diagnosis). Thrombo-infarctive black eschar is nowhere to be seen. The ulcer is enlarging by degenerative wet dissolution of tissues at the edge of the ulcer. The wound has inflammatory drainage, and the periwound has edema and erythema. This is the pure inflammatory-lytic pattern of injury. **Far right**, actively developing leg ulcers in a woman with rheumatoid arthritis. Likewise, there is no dry black eschar. Ulcers are enlarging by lysis. Periwound is erythematous and edematous. Distinctive of many autoimmune wounds is that the process is multifocal, starting as multiple foci of lysis, eventually coalescing into larger ulcers as in the adjacent image. This too is the pure inflammatory-lytic pattern of injury.

*These two patterns of ulceration, thrombo-infarctive and inflammatory-lytic, reflect something else profound about not just about wounds and tissues, but also evolutionary biology. Multicellular life depends not just on the aggregation and assembly of different cell types, but on speciation and specialization of those cells wherein is the source of complexity and adaptability. For this system to work as an integrated organism, there are two categorical necessities, (1) an architectural structural framework where special differentiated cells (epithelia and **parenchyma**) can bind together, and (2) a logistical transport and distribution network (the **stroma**) that allows parenchymal cells to deliver and receive items to and from each other. The generic stroma, common to all organized multicellular life of the Animal kingdom, is composed of and contingent on two, and only two cells, **angiocytes** and **fibroblasts**, and the fibrous and vascular structures that they make. Fibroblasts make the architectural structural framework using connective proteins. Angiocytes make the inter-exchange transport system in the form of a vascular network. Wound healing is nothing more than this stroma restoring itself, enough to re-establish the structural competence of the injured area and allow parenchymal cells to replenish themselves.*

*This stromal structure of multicellular life – **connective matrix** and **vascular distribution system** – was worked out from the beginning, about 1 billion years ago. The two key cells, angiocytes and fibroblasts, and the vessels and connective matrix they make, are so essential to multicellular life, that they cannot be safely altered. Collagen based structural forms are seen in the most primitive of multicellular organisms, the Porifera, the sponges. Evidence of a bulk transport system – a vascular system – is also seen in some sponges, and it is permanently established by the Cnidaria, the hydras and jellyfish. Because multicellular life is so categorically contingent on this **collagen-vascular stroma**, that once it was established, there was scant room for mutation. Key genes which organize these systems, such as VEGF which is the master regulator of angiocyte response and vessel formation, are highly conserved through evolution, having high homology between jellyfish and humans, and indeed the functional dynamics of VEGF on vascular cells and structures are identical for jellyfish and humans. Any mutation in these genes or cells would corrupt the stroma, thereby arresting the organization of the organism. The affected conceptus dies, and the bad gene cannot propagate.*

*Therefore, these cells, and the structures they make, have been thoroughly tested and debugged. They are essentially error free. These core infrastructure functions are so consistently conserved and dependable, so thoroughly robust, that there are no major genetic or metabolic disorders of the stroma or its two cells. Consequently there are no cellular pathologies of the mesenchymal component of wound healing. Why then are there wounds which cannot heal, wounds in which angiocytes and fibroblasts that should be restoring stroma are failing to do so? A thorough discussion is beyond the scope of this presentation, but basically, when wounds are sick or not healing, their cells usually are not intrinsically damaged or deranged. When they fail to function, it is due to some sort of exogenous stress, some sort of **deprivation** or **predation** affecting these cells and structures, there by hindering or disrupting the process from without. Two such exogenous stresses occur. Conditions of deprivation mean that cells cannot get the substrate they need, and since substrate is distributed via the vascular networks, deprivation is essentially synonymous with ischemia. Conditions of predation mean that some active agent is challenging or conflicting with the stromal cells. Absent extrinsic pathogens, internal predation comes from the immune system, auto-immunity, via lymphocytes and plasmacytes. The **thrombo-infarctive** pattern of injury represents ischemia from **vascular deprivation**. The **inflammatory-lytic** pattern of injury represents disruptive or toxic effects from **auto-immune predation**.*



8
Clinical Pathology of Hypercoagulable Wounds & Ulcers

Hypercoagulable wounds, ulcers, and infarcts present with distinctive and recognizable features. None of them are strictly pathognomonic, but they are consistent enough, and directly correlated with underlying pathophysiology, that the entire set of signs and symptoms take on a more or less syndromic consistency to their presentation. These features are easy to appreciate when doing an outpatient office evaluation of a hypercoagulable ulcer. However, these problems are also encountered "in the heat of the moment" when inpatient or post-operative or trauma patients start to have unexpected infarcts and wound complications. It is then that recognizing the following features will lead to proper diagnosis, treatment, and recovery.

Onset of Illness. Clots per se cannot be seen grossly, but tissues affected by micro-thrombosis will exhibit these telltale reflex changes during the acute or incipient phase. ***Signs of vascular stasis,*** in the form of pallor or else cyanosis from low flow and vascular dilation. ***Severe local ischemia of skin and fascias***, as evidenced by cool temperature, poor capillary refill, possibly hyperesthesia and tenderness (ischemic pain) or else hypoesthesia (infarct), cyanotic color changes, and postural rubor. ***Skin infarcts, progressing to ulceration***, appearance variable depending on time from event. ***Gross inflammation is plus-minus***, possibly present as a generic response to injury if surrounding or residual flow is sufficient, but often absent because flow is low or gone and the infarcted tissues are inherently not very pro-inflammatory. However, there may be ***pseudo-inflammation*** resulting from ischemic vasodilation with congestive plethora or stasis. The problem may be ***spontaneous versus triggered by a provocative event***, such as from injury, surgery, low flow states, or systemic or focal inflammatory states of immune, allergic, or suppurative origin. The event might be ***de novo or incidental***, or it could ***chronic or chronically recurring***. Like so many thrombo-infarctive and inflammatory-lytic lesions that lead to necrosis and ulceration, the process is ***common on the legs and ankles*** but ***can occur anywhere***, no place on the body categorically safe.

Link to Inflammation. Coagulation and inflammation are linked: Primary thrombosis triggers secondary inflammation. Primary inflammation triggers secondary thrombosis. Some injuries or responses reflect purely one or the other pathological domain. However, some wounds are inextricably mixed in both domains. In the presence of ***necrosis and ulceration***, observation of the ***thrombo-infarctive versus inflammatory-lytic*** patterns will clarify pathogenesis. Some events are purely thrombophilic, but others have a strong association with autoimmunity. The critical association with the CVD-CTD's goes both ways: active immune disease and chronic primary inflammation are an ongoing trigger for micro-

thrombosis, and sustained secondary inflammation for micro-infarction induces autoimmunity. Many patients have mixed autoimmune-hypercoagulopathic profiles, on both clinical and laboratory criteria.

Findings. Physical exam and laboratory evaluation are often distinctive, even if not pathognomonic. In addition to the signs of a low flow dysvascular state as listed above, other findings include: ***Ischemic infarction*** of skin, fascias, wounds, and even internal and visceral structures. Wounds might be established and old, but in the active phase, pure hypercoagulable disorders will create the distinctive ***thrombo-infarctive pattern*** of necrosis and ulceration. ***Edema and gross inflammation are often absent***. The ***periwound skin shows vascular stasis***. Wound and periwound almost invariably have ***low TcpO2's*** (or other similar technical measures of focal hypoxemia or hypoperfusion). ***Ischemic pain*** and tenderness are frequent. ***Wound module is mixed***, initially non-healing due to ischemia, but eventually recovering in the pure thrombotic-ischemic disorders, but not necessarily in those having an immune-inflammatory component. There will be ***no signs of other ischemic origins***, e.g. ***good pulses*** are present or ***TcpO2's are normal distal*** to the ulcer. ***Blood tests and histology*** can be confirmatory.

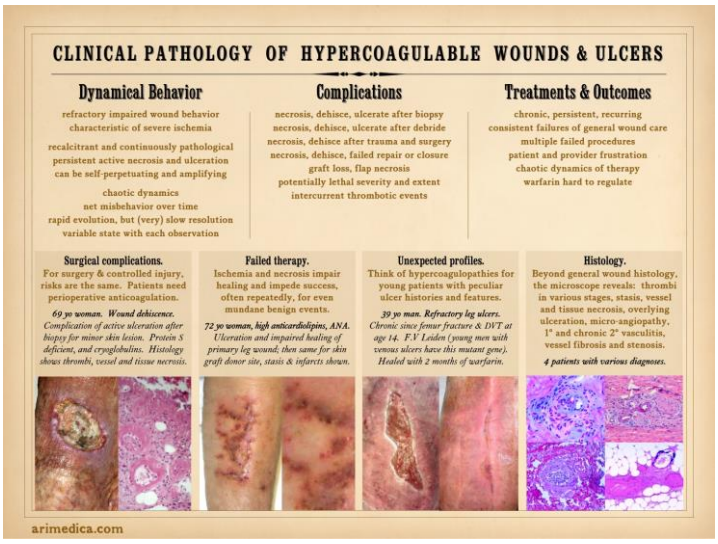
Examples of physical findings:

Case #1. Acute necrosis. 35 yo woman with acute lupus. Extensive skin infarcts (hips & thighs shown). Notice that beyond the eschars, the skin shows cyanotic stasis. Antiphospholipid antibodies. Low skin TcpO2s. For most patients, micro-occlusive and hypercoagulable skin infarcts are often small, scattered, and isolated or confined to small regions, but as seen here they can sometimes be large and life threatening.

Case #2. Stasis and infarcts. 43 yo man with spontaneous leg ulcers (leg & ankle shown). No large vessel peripheral vascular disease, good pulses. Very low proteins C and S. Around the established escharotic infarcts are zones of severe stasis which may die and ulcerate (or might recover). Histology shows small vessel thrombosis and organization, with adjacent stasis, congestion, and hemorrhage.

Case #3. Chronic active ulceration. 61 yo woman with protein S deficiency. Long history DVT, PE, and leg ulcers. Old recanalizing thrombus is shown, attesting to ongoing thrombosis. This is a chronic lesion, what happens after post-infarct eschar separates, leaving ulcers. However, the disease is chronically active, resulting in perpetual stasis, inflammation, and active ongoing infarction and ulceration, visible at the skin margins.

Case #4. Trauma pathergy, morbidity. 53 yo woman, rheumatoid arthritis. Dogbite of forearm, then many complications and failed repeated surgery. Proteins C & S deficient. Histology shows multiple occlusive and organizing thrombi. This is pathergy, wherein trauma and injury, in this case the dogbite then the surgery, trigger exaggerated microthrombosis, with unexpected wound infarcts, dehiscence, and failed repair.



9
Clinical Pathology of Hypercoagulable Wounds & Ulcers

The preceding panel on the clinical pathology of hypercoagulable wounds focused on distinctive features that can guide you to recognition and diagnosis, starting with *Onset of Illness*, *Link to Inflammation*, and *Findings*. This panel is a continuation of the subject with the categories *Dynamical Behavior*, *Complications*, and *Treatments and Outcomes*. That last section does not discuss treatment per se, but rather, as a matter of the clinical pathology of these disorders, how response to treatment is itself part of the clinical profile.

Dynamical Behavior. This refers to the behavior of the system in time, especially the non-instantaneous response to perturbation, whether it be an injury or trigger or else a treatment intervention. Blood coagulation is a complex multi-control system which will ipso facto exhibit chaotic variations in its various functions and parameters. These concepts are explained on a subsequent panel. What is important is that from a natural physics point of view, the coagulation system can seem stable, but under certain conditions, it can and will exhibit erratic and detrimental behaviors. Hypercoagulable wounds and ulcers will exhibit ***impaired wound behavior characteristic of severe ischemia***, meaning prone to spontaneous pathological progression (***persistent active necrosis and ulceration***), pathergy in response to intervention (***self-perpetuating and amplifying***), and refractory to ordinary care that works for normal non-ischemic tissues (***recalcitrant and continuously pathological***). Dynamical behavior is chaotic, seen as a variable state with each observation, often with rapid evolution of an unstable injured state but slow resolution or correction, and with aggregate misbehavior of the system over time.

Complications. The effects of ischemia, pathergy, and chaotic dynamics mean that complications are very prone to occur in response to diagnostic or therapeutic manipulations of the wounds and tissues. This mirrors the pathological misbehavior of these wounds as they are naturally evolving or failing. It is often these unanticipated complications that are the tipoff to a hypercoagulable state. Such events are necrosis, dehiscence, and ulceration after biopsies, debridements, and any trauma or surgery. Even if the patient had limited or none of this, or recovered from them in earlier phases of care, the seeming settled state of the latter wound is no guarantee that the same will not happen during subsequent wound repair or closure. Technically sound grafts and flaps can be lost or die. While you are focusing on the nominal "main event", intercurrent thrombosis or embolism can occur in unrelated areas, making even the most ordinarily simple or innocuous care of great potential severity or even lethality.

Treatments & Outcomes. The response to treatment in the presence of these disorders is often paradoxical to expectations and contrary to intent or benefit. This means both "response to treatment" of the primary malady that you are attending to, and response to antithrombotic therapies once the diagnosis is recognized. The problem you are treating, wounds or otherwise, might not respond to ordinary management for that

condition in the absence of the hypercoagulable state. Thus, the wound remains chronic, persistent, and recurring despite treatment. General wound care modalities will consistently fail. Surgery and other procedural activities will fail or cause pathergy, often repeatedly. Recognizing that reality is the way to avoid the trap of doing "too much too soon too often" (discussed on a subsequent panel). Repetitive failures lead to recurring disappointments for the patients, and ongoing frustration for the unwary clinician. Even when the diagnosis is recognized and accounted for, the chaotic dynamics of the system mean that response to treatment can be plagued by contrary and paradoxical results, too much, too littler, wrong direction, wrong effect or outcome. This is particularly notable in the efforts to regulate warfarin hard . We have limited options for anticoagulant therapies, and for many decades, warfarin (or similar dicoumarol derivative) was the one and only option for oral and outpatient use, so there was no way to avoid it. But because of its problematic pharmacodynamics and its narrow therapeutic index, warfarin must be individually regulated for each patient or problem. When given to a patient with a normal coagulation system, such as for atrial fibrillation, it can be relatively easy to find and maintain a stable therapeutic dose. Not so with the hypercoagulable disorders. Their chaotic nature means that warfarin doses and the prothrombin times will exhibit the same erratic and "hard-to-hit-the-moving-target" dynamics that frustrate the rest of the clinical care.

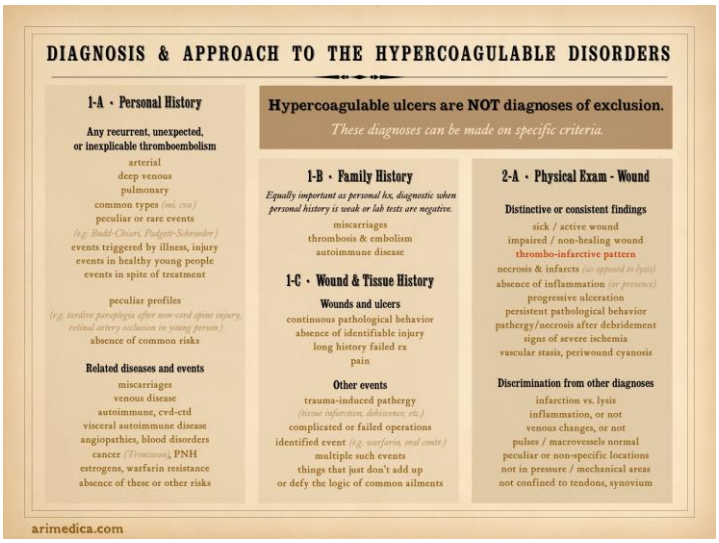
Examples of physical findings:

Case #5. Surgical complications. 69 yo woman, wound necrosis and ulceration after seemingly innocuous biopsy of skin lesion. Good foot and ankle pulses. Protein S deficient, also cryoglobulins present. Histology shows thrombi in vessels, with vessel and tissue necrosis. Thrombosis risk is same for surgery and procedures as for uncontrolled trauma. In patients known to have these disorders, they need perioperative anticoagulation.

***Case #6.* Failed therapy.** 72 yo woman with chronic ankle wound. Improvements with basic care led to skin grafts which paradoxically caused new wound infarcts plus stasis & infarcts at skin graft donor site (shown). High anticardiolipins, ANA. On the afferent injury side of wound dynamics, ischemia causes infarcts. On the efferent healing side, it impairs healing, impedes success, often repeatedly, for even mundane benign events.

***Case #7.* Unexpected profiles.** 39 yo man, refractory leg ulcers since femur fracture & DVT at age 14. Lab: factor V Leiden. Healed after 2 months of warfarin. Femoral vein thrombosis after fracture is not rare but not ordinary. This should prompt suspicion of a hypercoagulable state, especially in a juvenile. For young people with venous stasis ulcers or other peculiar history, mutant f.V Leiden or other hypercoagulopathy is often present.

***Case #8.* 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. Thrombosed and micro-occluded vessels are illustrated in 4 specimens from 4 patients with various diagnoses (top, mixed auto-immune; bottom left, proteins C & S; bottom right, hyperparathyroidism).



10
Diagnosis & Approach to the Hypercoagulable Disorders

This and the following panel discuss the diagnostic approach to the wound or the patient with a hypercoagulable disorder. Like any other problem in medicine, diagnosis is arrived at by history, physical exam, and the laboratory. For these disorders, history of the wound (or whatever the index problem is), personal medical history, and family history are all equally important and must all be addressed. Physical exam of the whole person is equally important as exam of the wound. Because wounds are dynamical systems that evolve, their timewise behavior and response to treatment are also essential parts of the ongoing exam. It is vital to appreciate always that ***the hypercoagulable ulcers are NOT diagnoses of exclusion***. They can be made on specific criteria. If you are new to this subject, the tetrad-pentad of the Hypercoagulable Syndrome is always a convenient and easily remembered framework to guide the rest of the history and physical.

Also keep in mind the distinction or the duality of hypercoagulable or hyperthrombotic ***disorders versus states***. This concept is discussed in greater depth elsewhere, but it is worth keeping in mind during the initial diagnosis of the patient. ***Hypercoagulable disorders*** can be considered the underlying primary factor, the root of the system that leads to abnormal intravascular thrombosis. If could be a inborn gene mutation such as factor V Leiden, or it could be an acquired disorder such as liver disease or warfarin administration causing a plasma protein imbalance, or an immune procoagulant bred by an autoimmune connective tissue disorder. ***Hypercoagulable states*** are the momentary periods when the balance of coagulation factors favors abnormal or accelerated thrombosis. The two concepts are obviously related and mutually contingent, but they are not synonymous. Even people with built in root cause hypercoagulable species are not always in a hyperthrombotic state. They can seem normal at times. This is due to the nature of coagulation as a complex non-linear multi-control system. This causes chaotic dynamics which means that at times the system might dwell in a stable basin of normal behavior. Depending on other concurrent stress, illness, inflammation, injury, and dietary and metabolic factors, the blood can settle to seeming normality, or get stirred up for longer or shorter epochs of hyperthrombotic tendencies or more irritable trigger sensitivity. Understanding this can make a patient's history more sensible if it seems variable over time or circumstances.

1-A • Personal History. These features from the patient's personal history should raise suspicion of a hypercoagulable state. There are two groups of such features, thrombosis events per se, and disorders that cause or result from clotting. ***(1) History of prior clots*** is especially notable if there have been ***recurrent, unexpected, or inexplicable thrombotic or embolic events***: they can be arterial or venous, peripheral or central, primary or embolic; they can be common large vessel events such as MI or CVA; they can be peculiar or infrequent macrovascular events such as Budd-Chiari or Padgett-Schroeder; events triggered by incidental or intercurrent illness or injury; events in otherwise healthy young people ; events in spite of usual treatment following prior such thrombotic or embolic events; peculiar profiles of illness such as tardive paraplegia after non-cord spine injury

or sudden blindness in a young person due to retinal vascular occlusion; and finally, absence of common risks such as atherosclerosis or atrial fibrillation or an established diagnosis of immune arteritis. (2) ***Associated disorders that either cause or result from*** the coagulopathic state are an alert to hypercoagulability. These include miscarriages, chronic venous disease of the legs, autoimmune cvd-ctd's, visceral autoimmune disease (liver, kidney, thyroid, etc.), non-atheromatous angiopathies, formed element or other micro-occlusive blood disorders, cancer and paraneoplastic syndromes such as Trousseau, PNH paroxysmal nocturnal hemoglobinuria, early liver disease, use of estrogens, and warfarin resistance. Also important is the ***absence of these and similar risks***. For example, leg and ankle ulcers can be due to venous or macro-arterial disease. Not seeing the usual signs of venous disease (pigment changes, liposclerosis, dermatitis, edema), or having normal palpable pulses rules out those disorders, placing hypercoagulable lesions higher on the differential diagnosis. In taking the personal history, be sure to run the list of the Hypercoagulable Syndrome, asking about prior thrombosis or embolism, miscarriage, autoimmune disorders, and other events of ulceration or wound pathergy.

1-B • Family History. Family history is the fifth element of the Hypercoagulable Syndrome, and it is equally important as personal history. In taking family history, use the syndromic tetrad as the basis for questioning, "Have you are anyone in you family ever had clots, miscarriages, rheumatoid or lupus, or wounds or surgery go bad?" As one of the key features of the syndrome, family events can be diagnostic when personal history is weak or lab tests are negative.

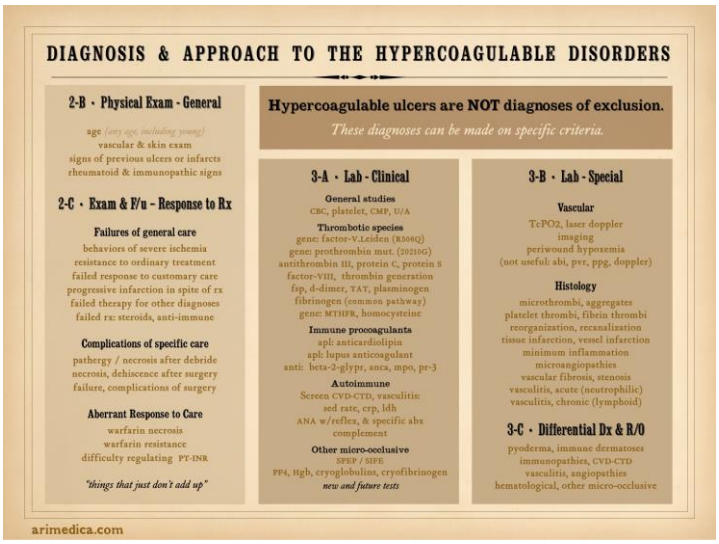
1-C • Wound & Tissue History. All chronic, problem, pathological, and non-healing wounds require proper history and assessment of the underlying causative disorder to arrive at correct diagnosis and treatment. The converse is also true, that to understand and treat condition Abc which is causing the wound or any other sequelum, those manifestations of the primary disease must be carefully evaluated. When a hypercoagulable or other micro-occlusive disorder is suspected, the following features of the wound are consistent. **Wounds and ulcers.** Wounds are there, active and misbehaving, in the ***absence of an identifiable injury*** such as trauma. These will have shown or continue to show ***continuous pathological behavior***, usually despite treatment. Indeed, there is often a long and repetitive ***history of failed treatment***, and the longer the wound has persisted, the longer the history of failed therapy. There can be a history of ***contrary or paradoxical responses*** to treatment that worsen the wound. ***Pain*** is a characteristic feature, due to ischemia. Ordinary healthy wounds do not have pain (discounting the original pain at time of injury). There are only several classes of morbidity that make pain, including trauma and mechanical effects, inflammation, ischemia, neuropathic types. For ischemic conditions, pain is typically the predominant symptom, sometimes the only one, such as angina pectoris from coronary artery disease, exercise induced pain (along with claudication) in atherosclerotic extremities, pain from compartment syndromes, even pain with tourniquet use during extremity surgery (pain typically manifest within 15-20 minutes of cuff inflation). Wounds exhibiting the inflammatory-lytic pattern of injury are also often painful because they are due to active inflammation. In the thrombo-infarctive pattern of injury, end-stage dead eschar has no pain. This is comparable to burn injuries in which full thickness "third degree" damage has no pain or sensation because nerve ends in the affected dermis are also dead. However, in the ischemic but still viable wound, exhibiting all the signs of the thrombo-infarctive pattern of active injury, including vascular stasis, ischemic vasodilation, rubor or cyanosis, cool temperatures, and lack of edema or signs of desiccation, these wounds will have pain. Tenderness may be present, sometimes not, but pain is typical, due to the ischemia.

Other wound related history. Other historical features or events that indicate a thrombo-infarctive or hypercoagulable wound include ***trauma-induced pathergy*** (tissue infarction, dehiscence, etc.) for other or prior wounds as well as the one in focus, including ***complicated or failed operations***, especially multiple or a series of such events. There can be other ***identified triggers or antecedent events*** such as starting warfarin therapy or oral estrogen based contraceptives. Any of these things could have been isolated or incidental events for other reasons, but when there have been ***multiple such events***, hypercoagulability is suspect. Finally, when items of this nature seem to ***defy the logic of common diseases***, or the miscellaneous features ***"do not add up"*** in expected ways that lead to diagnoses or pathophysiologies that you are familiar with, then there is some other operative at work which warrants consideration.

2-A • Physical Exam – Wound. Physical examination provides many ***distinctive or consistent findings*** that can identify thrombotic micro-occlusion, due to hypercoagulability or other reasons, as the cause of the wound, either its original onset or its abnormal persistence. These are often ***"sick" or active wounds***, meaning that they are not just static or persistent ulcers but rather, despite efforts to treat, they remain actively pathological, actively causing new infarcts and progressive ulceration. Alternately, they may have passed into a more settled or quiet downstream phase with features of the ***impaired and non-healing wound***, not currently exhibiting overt infarcts or active-progressive ulceration but sufficiently present to impede self-assembly and structural improvements in the wound. The ***thrombo-infarctive pattern*** consistent with macro- or micro-ischemia will be present, and to the extent that it is "pure" ***necrosis & infarcts lacking inflammatory lysis***, that strengthens the diagnostic certainty. Explicit ***absence of inflammation*** despite obvious injury and ulceration is noteworthy. However, the opposite, the ***presence of inflammation***, can also be indicative of hypercoagulable wounds because there can be enough residual flow to ensure a proper inflammatory response to the micro-thrombotic tissue injury. The ***signs of severe ischemia***, such as vascular stasis, cyanosis, and these other markers of hypoxia and restricted blood flow need not be confined to the wound itself. The can extended ***beyond the wound to the periwound***, a few millimeters or a few centimeters outward, or sometimes in large regional areas if thrombosis has affected larger vessels. Also, wounds are dynamical entities, and they evolve in time. A one-time static exam of a wound is generally insufficient to learn what is really happening. Thus, not as a matter of history, but as observed on your own ***serial or sequential exams***, you are apt to see ***progressive ulceration*** and ***persistent pathological behavior*** from one exam to the next. ***Pathergy and necrosis after debridement*** will be not just a matter of history, but a followup observation after your own hands-on activity.

Most of these signs and symptoms are not pathognomonic of hypercoagulability or micro-occlusion. They simply reflect a heightened or sustained state of injury, inflammation, and ischemia from a many possible causes. How does one ***discriminate these diagnoses from other disorders*** based on physical exam features? ***Infarction versus lysis*** as the vector of ulceration is always helpful. ***Inflammation or not***, as explained above, must be analyzed. ***Venous changes, or not***, are important – liposclerosis, pigment deposits, chronic edema. Absence means that ordinary "venous stasis" is not present, so simple hemodynamical venous hypertension and reflux are not implicated as cause of the ulcer, so seek an alternate diagnosis. However, many chronic venous cases are from prior venous thrombi, which in turn some or many are due to hypercoagulability, so correlating venous signs with other features on history and exam may reveal hypercoagulability. On the arterial side, ***presence of pulses*** means that these patients are having signs of arterial ischemia but macrovessels are normal and flowing. This is in distinction to classic arterial diseases where pulses are absent. Areas affected, exhibiting cyanotic ischemia and infarction, may be in ***peculiar or non-specific locations***. For example, foot ulcers might imply possible lower body atherosclerosis, but lesions that appear in seemingly random places on the trunk or proximal extremities cannot be

attributed to ordinary macro-angiopathies. Likewise, pressure ulcers occur in distinctive pressure loaded zones, so when ischemic skin occurs elsewhere ***not in pressure or mechanical areas***, those diagnoses are excluded. Even other pathological wounds, especially rheumatoid, lupus, and other autoimmune cvd-ctd's, can have distinctive distributions of their inflammatory-lytic ulcerations, such as along tendon sheaths and retinacular ligaments, so when other lesions appear that are not confined to tendons or synovium, that helps favor non-immune diagnoses



11
Diagnosis & Approach to the Hypercoagulable Disorders

This panel continues the topic from the last one, the diagnostic approach to hypercoagulable disorders and wounds. Diagnosis is arrived at by history, physical exam, and the laboratory. This includes personal medical history (1A), family history (1B), and history of the presenting wound or index problem (1C). Examination of the wound is essential (2A), but so is exam of the whole person (2B), and then sequential ongoing exam (2C). ***The hypercoagulable ulcers are NOT diagnoses of exclusion. They can be made on specific criteria.*** The tetrad-pentad of the Hypercoagulable Syndrome is always a useful framework to guide the rest of the history and physical.

2-B • Physical Exam – General. Always examine the whole person. ***Age is important.*** Hypercoagulable ulcers can occur at any age. However, otherwise healthy young people (children, teenagers, young adults), are less prone to have ulcers and failed wounds from common adult causes such as vascular disease or diabetes, so always look for an occult etiology, such as juvenile onset rheumatoid or similar immune disorders, or else micro-occlusive disorders. Young people should not have venous disease, so when they do, be suspicious of a hypercoagulable disorder, especially one of the relevant gene mutations. General ***vascular and skin exam*** might reveal telltale signs of the underlying disorder because of manifestations outside the ulcer zone or the overtly affected extremity. ***Signs of previous ulcers or infarcts*** will reveal if this has been a long standing or ongoing problem, and whether or not prior lesions healed, healed easily, healed with difficulty, have recurred, still persist, or have residual concerns. Crucial is to look for signs of ***rheumatoid, lupus, and other immunopathic states***. These might be the very first things observed on the patient encounter, such as noticing that the hands are crippled (rheumatoid) or sclerotic (scleroderma), or that the patient has a distinctive malar rash (lupus) or periorbital heliotrope rash (dermatomyositis), or holding a bottle of water for dry mouth (sicca, Sjögren's).

2-C • Exam & F/u – Response to Rx. As mentioned on the last panel, serial or sequential exam is essential to proper diagnosis of wounds, as well as monitoring response to treatment and progress toward resolution. Various features of physical exam are indicative of ongoing and unresponsive conditions. ***Failures of general care*** are common, wounds that fail to improve with the basics of topical hygiene and edema control. ***Resistance to ordinary treatment*** and ***failed response to customary care*** are tipoffs that there is some underlying pathological state that is active and needs treatment. Wounds continue to exhibit ***behaviors of severe ischemia*** (signs of arterial stasis, failing to heal, sensitive to injury) while exhibiting ulcerative pathergy with ***progressive infarction in spite of treatment*** or actually due to debridement or other manipulation. ***Progressive infarction in spite of therapy*** means either that the current diagnosis is wrong, ***failed therapy for other diagnoses***, and thus hypercoagulability or other alternate must be considered, or else that even with a correct diagnosis, current treatment is inadequate and needs adjustment. Since so many pathological wounds, which are due to autoimmunity or hypercoagulability or related inflammatory and hematological disorders, have a mixed or cross-over pattern of features on history, exam, and lab profile, discriminating them can be a challenge. If diagnosis was presumed to be primarily inflammatory, but first line ***steroids or anti-immune treatment failed***, with persistence of coagulopathic signs and symptoms, that strongly favors switching to the alternative domain and starting anticoagulant therapies.

Not only can various treatments fail to get the desired results, but if a hypercoagulable state persists and remains untreated, there are likely to be ***complications of specific care***. This is largely a corollary of the pathergy concept, and the "specific" items of care at risk are typically procedural, in which well meant therapeutic injury triggers more of the thrombosis and cascade and the thrombosis-coagulation circuit. These scenarios are typically ***wound pathergy or necrosis after debridement***, ***necrosis and dehiscence after surgery***, and similar ***failures or complications of surgery***. Pathergy and surgical complications are unfortunate, but there is never any lapse in identifying the problem. A procedure is done, the incision dies, the wound falls apart. The chain of events is undeniable. However, non-surgical interventions can also cause problems, such as drugs, but since there might be a phase lag or hysteresis between prescribing the care and seeing the adverse result, the association might be overlooked, especially if the intervention was seemingly innocuous or meant to induce an improvement or correct the hypercoagulability itself. ***Aberrant responses to care*** are perhaps most common and obvious with respect to warfarin use. Warfarin works by reducing plasma protein production by the liver, but in the early phase of treatment, the drop in factors can be unbalanced leading to a state of hypercoagulability, manifest as ***"warfarin necrosis"*** with random skin and soft tissue infarction anywhere on the body. That type of imbalance and contrary response is more likely to occur in patients with thrombophilic or other hypercoagulable disorders, which will be better understood on the subsequent panels about coagulation dynamics. For those same dynamical reasons, it is also ***difficult to regulate warfarin treatment***. Finding a stable dose, as measured by the prothrombin time (or its normalized form PT-inr), is notoriously difficult or virtually impossible with the thrombophilic and hypercoagulable disorders. There are also many such patients who exhibit ***warfarin resistance*** in whom a therapeutic dose cannot be found at ordinary levels, for example giving 20 mg daily and still not seeing a budge in the PT-inr. When ***"things just don't add up"***, when the logic of treating ordinary wounds or ordinary anticoagulant therapy results in ineffectiveness, resistance, and contrary responses, look for the hidden gremlin in the system

3-A • Lab – Clinical. As for any other clinical condition, the laboratory can be most useful for confirming a tentative diagnosis or elucidating an uncertain differential, analyzing or understanding the state of the system or its pathological behavior, or monitoring response to treatment. It can also be confusing or uncertain, and there are times when one cannot ascribe too much significance to an out-of-range variation, and other times

when a positive diagnosis must be made on clinical criteria while ignoring a negative laboratory workup. Knowing how to interpret each test is thus important. Blood tests that can establish or assist in the diagnosis of the hypercoagulable disorders can be grouped into several categories based on physiological significance. Remember, we only have a finite number of established clinical chemistry tests that support the diagnosis of hypercoagulable disorders. We cannot readily measure any protein or factor we want to, just those that are offered by the lab. **General studies:** CBC, platelets, complete metabolic panel, and urinalysis provide the same general body screening that makes them valuable for sniffing out an insight to any type of major organ pathology. Blood counts are especially important due to the integration between formed elements, marrow functions, and the plasma proteins. Any abnormalities should be pursued further to establish a proper diagnosis, even though frequently that will veer toward the non-hypercoagulable hematopathologies. **Basic clotting studies:** These are usually not relevant. Ordering them reflects habits that arise from the bias that clotting disorders or their treatment are on the hypocoagulable side. Prothrombin time, useful for monitoring the effects of heparins, and Quick's prothrombin time, usually used to monitor warfarin therapy and liver disease, are diagnostically altered (prolonged) in hypocoagulable states. For hypercoagulable states, these values are irrelevant or uninterpretable. Compare, for instance to sodium, potassium, and glucose where out of range levels are meaningful on both sides, over and under. In contrast, PT and PTT and similar tests are comparable to uric acid or transaminase levels where under-range values generally mean nothing. **Thrombotic species:** These are the chemicals of the main sequence plasma protein system or closely allied cofactors, the direct mediators or regulators of thrombosis. These include two altered genes, factor-V.Leiden (R506Q), and prothrombin mutation (20210G), factor VIII, fibrinogen, and thrombin-generation as an functional assay of coagulation capacity. **Indicators of prior or active thrombosis:** Some of these directly detect thrombosis by its degradation products and reflexes: fibrin split products (fsp), d-dimer, plasminogen. Others show reflex upregulation of endogenous anticoagulants, presumably a feedback response of the system to detecting a state of elevated or aggravated thrombosis: antithrombin III, protein C, protein S, thrombin-antithrombin (TAT) complex. **Metabolic procoagulants:** homocysteine, and mutant gene MTHFR (methylene tetrahydrofolate reductase) which indirectly regulates homocysteine. **Immune procoagulants:** the antiphospholipid antibodies (anticardiolipins, lupus anticoagulant, anti-beta-2-glycoprotein); the ANCA's (anti-neutrophil cytoplasmic anti-bodies, or anti-cytoplasmic autoantibodies), including anti- myeloperoxidase (mpo) and proteinase-3. **Autoimmune screen:** general signs of active inflammation (sed rate, C-reactive protein crp, lactate dehydrogenase ldh); screens for autoimmune cvd-ctd's and vasculitis (ANA with reflex, or the individual specific antibodies, e.g. dsDNA, SSA, SSB, rheumatoid factor, and anti-chromatin, rnp, centromere, mitochondrial, ccp, etc.); complement, and serum proteins and immunoglobulins (spep and sife electrophoresis). **Other micro-occlusive species:** para-proteinemias (cryoglobulins, cryofibrinogen, spep, sife); hemoglobinopathies, platelet pathologies (including adhesion-aggregation studies, anti-PF4).

There are always new and future tests that appear. General medical literature is always relevant for updating awareness of new tests, but perhaps the easiest means to learn about new coagulation or other tests is from the catalogs that commercial clinical labs publish. Every two or three years there is likely to be another test or two that appears, perhaps one from the coagulation side and one from the auto-immunity side, test that are useful for workup and management of hypercoagulable disorders, patients, and wounds. The next panel includes a table with interpretations of some of these tests.

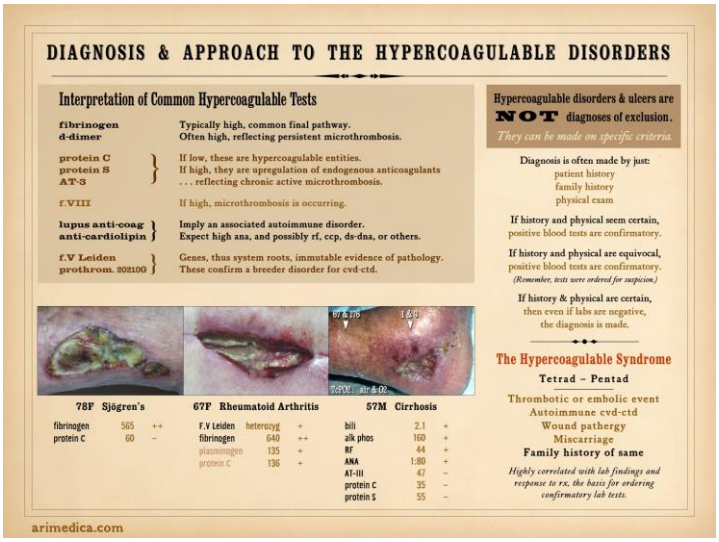
3-B • Lab – Special. Certain specialized testing and laboratory studies are extremely useful in the diagnosis and management of wounds and hypercoagulopathies. These are mostly vascular studies and histological study of biopsied or excised specimens. **Vascular:** The key goal of vascular assessment when approaching micro-occlusive wounds is to confirm that there is capillary or small vessel occlusion and ischemia by showing (1) that the affected wound and tissues are hypoperfused or hypoxic, (2) that beyond the periwound there is normal perfusion, and (3) that the changes cannot be attributed to macrovascular disorders. The most useful measure of hypoxia or ischemia is ***TcpO2's***, transcutaneous partial pressure of oxygen. The pickup is a small fluid filled chamber with a semipermeable membrane placed against the skin allowing oxygen diffusion into the chamber where its partial pressure can be transduced. It is simple and painless, albeit somewhat time consuming. Meaningful measures come from placing the pickup at various places in the affected zone, looking for ***wound and periwound hypoxemia***, but also in normal reference areas on thigh or trunk or other superior parts of the body, and also on distal parts when possible, looking for normal oxygen. Example, finding very low pressures at the wound edge at the ankle, and in any seeming low flow stasis areas, and then finding normal values on the dorsal foot and toes confirms that the lesion is due to something other than atherosclerotic large vessel inflow disease. Similarly, infarcted skin lesions of the trunk due to hyperparathyroidism will have low TcpO2's at those lesions but not elsewhere that skin looks normal such as other areas of the abdomen or anywhere else. This test is equally valuable for ischemic wounds of any cause, such as atherosclerosis (e.g., from hypertension or diabetes) or autoimmune vasculopathy (e.g., lupus or scleroderma). This means that clinical context is all important in determining treatment, but the interpretation of the test is the same – it identifies wounds that are ischemic from arterial low flow. Key to the hypercoagulable findings is that the wound ischemia is a local phenomenon at each lesion, other areas are not affected. TcpO2 is also a practical monitor of treatment and recovery, with wound or periwound values rising as patient and wound status improve.

Direct ***studies of flow or perfusion*** are available but not so universally utilized as TcpO2's. The discrepancy is not due to the techniques or value of the information, but mostly because of economics and the costs of the machines. Unlike TcpO2, vascular flow measuring devices typically have very large "sticker prices" and have achieved only a small market. If available, they can be useful, although the information and derivative clinical decisions are generally comparable to TcpO2. They include technically proven but clinically unwieldy technologies such as laser doppler and implantable hot wire anemometers. More practical but expensive are no-touch and tracer-injection imaging technologies such as thermography, multispectral image processing, and tracer imaging (usually indocyanine green, icg). They measure blood flow, not oxygen, so they do not necessarily mean the same thing, but the information is comparable to TcpO2, and comparably relevant to make diagnostic and therapeutic decisions, and they give a broader data set useful for academic investigation. The ultimate value of these methods is that they can image and compare affected and unaffected areas, good and bad areas. In that sense also they are like TcpO2's, but they can capture all data simultaneously and thus are more efficient and thorough than TcpO2. One test measures oxygen, the others measure flow. If both are available, the combination makes for a more robust and finely tuned diagnosis. Certain flow tests from the vascular lab are ***not useful, bulk flow or large vessel tests*** such as comparative blood pressures (ankle-brachial indexes, abi's), pulse volume recordings (pvr), photoplethysmography (ppg), and doppler's (pressures and imaging). These tests are made for the diagnosis and management of large vessel diseases. For micro-occlusive wounds, they can be useful in that they confirm the absence or coincidental presence of large vessel problems, thereby restoring the diagnostic focus to micro level things, but the data they yield is not usually relevant to hypercoagulable diagnosis and treatment monitoring.

Histology: There are three broad domains of information which can help establish a hypercoagulable wound diagnosis. First is history and physical exam, centered around the pentad of the hypercoagulable syndrome. Second is the clinical lab profile and the blood tests listed above. The third is the wound histology. When all three are positive, diagnosis is unequivocal, and generally so too when two of three are positive. However, each of these domains is sufficiently relevant that when even just one is positive, the diagnosis can be established. Thus, a patient might have a suspicious looking ulcer and exam, but hypercoagulable pentad history is negative, and lab tests are negative, but if the microscope reveals the following then the diagnosis can either be made or at least left on the differential diagnosis for further consideration. Examination of biospies or debrided material will reveal these following features. Small vessels have ***intraluminal microthrombi or microaggregates*** of thrombotic and cellular material. ***Platelet and fibrin thrombi*** can also be seen, at times without red cell clumping, and the type of thrombus can thus be relevant to the diagnosis of the particular species of micro-occlusion. Thrombi can be present in various stages of evolution from raw fresh fibrin and erythrocytes to varying degrees of inflammation, consolidation, fibrosis, ***reorganization, and recanalization***. The effects of thrombotic ischemia can be seen as ***tissue infarction*** and even ***infarction of the vessels*** themselves. Inflammation is the general response to injury, and inflammation will be worse when immune and inflammatory disorders are the primary problem, but when hypercoagulability caused the injury, there is often ***minimum inflammation***, partly because it is not a primary inflammatory disorder, but also because flow restriction limits the transport of leukocytes to the site. Distinctive ***microangiopathies***, typically due to unrelated diagnoses, present thrombogenic surfaces on which blood can clot, especially hypercoagulable blood (e.g., the calcific medial arteriosclerosis of secondary and tertiary hyperparathyroidism, associated with thrombosis and ulceration, and frequently having fibrin and solid thrombi). ***Vascular fibrosis and stenosis*** can occur as injured and thrombosed areas heal and develop proliferative changes and scar, often having atheromatous like features but usually without calcifications. ***Vasculitis, acute (neutrophilic)*** can be present (e.g., leukocytoclastic vasculitis, polyarteritis nodosa) which may be of unrelated origin (e.g., autoimmune disorders) but which render the vessels thrombogenic, the risk of actual thrombosis amplified further in the face of hypercoagulability. ***Vasculitis, chronic (lymphoid)*** can be present as a result of autoimmunopathies, creating conditions prone to activation of neutrophils and thrombogenic acute inflammation, and also promoting chronic fibromuscular hyperplasia (scleroderma type) which restricts flow channels and vascular compliance which are coagulation risks further heightened in the face of hypercoagulability.

3-C • Differential Dx & R/O. To reiterate, few or virtually none of the features of hypercoagulability, signs, symptoms, lab tests, histology are unique to or pathognomonic of the thrombophilic or hypercoagulable disorders. The gene mutations (V Leiden and prothrombin) might qualify, but there is nothing like the distinctive histology or lab studies that establish diagnoses such as sickle cell disease or thalassemia or spherocytosis which are also micro-occlusive disorders that cause chronic ulcers and wound pathergy. Therein is one of the reasons why the hypercoagulable disorders remain underappreciated – the diagnosis cannot be defined or pinned down by a single test or metabolic interaction, and thus the syndrome and physiology are hard to clarify. A monoclonal gammopathy on protein electrophoresis has a somewhat diverse differential diagnosis, but just knowing "monoclonal gammopathy" puts you on the proper diagnostic trail. High uric acid or morning cortisol levels by themselves establish a diagnosis or very limited differential. Knowing that bilirubin is high will lead you rather easily to find the actual disease. A high creatine says "renal failure" with little equivocation. Not having anything of that certainty in the realm of hypercoagulability has made it historically hard to even crystallize the concept let alone commit it to textbooks and student teaching.

As a practical matter, seeing a patient or wound with hypercoagulable features means you are seeing non-exclusive non-pathognomonic features, and thus the differential diagnosis must be worked to a final resolution. The hypercoagulable diagnoses can be made on positive criteria, but you must still exclude items that are very similar. Ultimately, with the hypercoagulable syndrome pentad as a guide, the preponderance of features in you workup will lead to the diagnosis. To get there though, you must be certain that you are not dealing with inflammatory and immune dermatoses or pyoderma gangrenosum or panniculopathies, systemic immunopathies and cvd-ctd's, inflammatory angiopathies, metabolic and degenerative angiopathies, formed element and other non-plasma hematopathologies or other micro-occlusive conditions, and any other disorder that affects or injures or activates inflammation, immunity, vascular disease, coagulation, and other blood disorders.



12
Diagnosis & Approach to the Hypercoagulable Disorders

This panel explores how to take the many pieces of relevant information and try to formulate the final diagnosis. Remember, hypercoagulable disorders & ulcers are NOT diagnoses of exclusion. It may be necessary to rule out similar items on the differential diagnosis, but hypercoagulable states can be diagnosed on specific criteria. Diagnosis can be made by clinical features (patient history, family history, and physical exam) or by laboratory features (clinical lab, histology), or both.

The framework for taking the history will be the tetrad-pentad of features of the **Hypercoagulable Syndrome:** thrombotic or embolic event, autoimmune cvd-ctd, wound pathergy, miscarriage, family history of same. A positive profile will be the basis for ordering confirmatory lab tests, and typically the tests will correlate well with the lab findings and subsequent response to treatment.

To establish the diagnosis, oftentimes the clinical encounter alone will suffice. ***If history and physical are equivocal***, then blood tests are necessary, and positive blood tests are confirmatory (remember, the tests were ordered for a strong suspicion). ***If history and physical seem certain***, then positive blood tests are not essential, but it is still useful to get them, to see the objective confirmation, but especially to identify the species which will have bearing on the details of treatment and prognosis, especially for the long term. ***If history & physical are certain***, but lab tests come up negative, the diagnosis is still made (recall that we have only about 2 dozen tests for a system that has scores or hundreds of actors). It is uncommon though that tests will all be negative. If history is strong, then not seeing a positive test is unlikely, so if blood tests fail to score, then

histology will, or vice versa. If despite a strong history there is a ***perfectly clean laboratory profile*** which causes you to call the diagnosis into question, then workup should shift to the alternative micro-occlusive disorders and other causes of wound pathergy.

Presented are three cases illustrating laboratory profiles typical of those often revealed.
Patient 1 is a 78 year old woman with Sjögren's. Despite clinical history of an autoimmune disorder, the ankle ulcer has a distinctively pure thrombo-infarctive pattern with no inflammatory changes in the periwound. Only two tests were abnormal: fibrinogen = 565 high, and protein C = 60 low. Fibrinogen is a common final pathway for hypercoagulability in many such patients, and low protein C is a primary hypercoagulable species (as an endogenous anticoagulant, low values dis-inhibit the thrombogenic tendencies of blood). This profile is a strong correlate of the physical findings.

Patient 2 is a 67 year old woman with rheumatoid arthritis. This post-operative back wound has extensive necrosis and vascular infarction. There is some edema and erythema, but it is not much, more consistent with normal post-operative status than active autoimmune disease. Laboratory profile correlates well, consistent with a primary coagulopathy rather than auto-inflammation. She has: factor V Leiden = heterozygous (a built in genetic root of the problem), fibrinogen = 640 high, plasminogen = 135 high, protein C = 136 high. Here too, we see high fibrinogen as common pathway, not surprising in the face of the gene mutation and the wound activation by surgery. Plasminogen is high, reflecting upregulation in response to thrombosis (its purpose being to degrade fibrin and maintain balance in the blood). Unlike Patient 1, protein C is high, representing a reflex upregulation of the endogenous anticoagulants in response to a thrombogenic or thrombotic state.

Patient 3 is a 57 year old man with cirrhosis of uncertain origin. Retro-malleolar ulceration is a common location for lupus and auto-immune wounds, but this wound has a mostly thrombo-infarctive pattern, including small infarcts and cyanotic vascular stasis. Periwound edema is present but mild, and scarlet red erythema of acute inflammation is absent. Lab shows: bilirubin = 2.1 high, alkaline phosphatase = 160 high, rheumatoid factor = 44 high, anti-nuclear antibodies = 1:80 high, antithrombin-III = 47 low, protein C = 35 low, protein S = 55 low. Bili and alk-phos confirm liver disease. Mild but non-trivial rises of RF and ANA confirm an autoimmune disorder (which could imply autoimmune hepatobiliary disease, but not confirmed by positive serologies). All three endogenous anticoagulants, AT-3, prot C, prot S are low, thus not upregulated in response to a hypercoagulable state, instead all low causing a hypercoagulable state. Their low numbers can be attributed to his liver disease. Immune procoagulants are not present, and with the wound being almost purely thrombo-infarctive, an autoimmune state is less likely to be causing his hypercoagulability or contributing to pathogenesis of the wound. Instead, his lupus profile reflects secondary autoimmunization from breeder effects of the hypercoagulable state. Knowing he has palpable pulses, the diagnosis of micro-occlusion is confirmed by low TcpO2's. In a skin area free of any stasis a few centimeters superior to the malleolus, TcpO2's are normal with room air pO2 = 67 torr, response to 100% oxygen breathing also normal = 176%. In contrast, in the stasis zone adjacent to the ulcer, the values are room air = 01%, oxygen challenge = 03%, a virtually unequivocal indicator of micro-thrombosis.

As illustrated, various laboratory test reflect a range of physiological or pathological states, and certain lab values can vary high or low with different relevant interpretations. There is no such thing as a "hypercoagulability test". Each species must be ordered and interpreted individually, then analyzed as a group, then evaluated in context of the clinical profile. Here are some of the commonly altered tests and what they mean: ***fibrinogen*** is typically high in hypercoagulable states representing a common final pathway for many of them; ***d-dimer*** is often high, serving as an indirect marker of active or persistent microthrombosis; ***protein C, protein S, and antithrombin-3*** are the endogenous anticoagulants, and when low they cause thrombosis, but when high they reflect active microthrombosis, having been upregulated to counteract thrombosis caused by other species; ***factor VIII*** is a main sequence plasma protein with a particular tendency to provoke clotting which is likely occurring when this factor is high. The antiphospholipid antibodies, ***lupus anti-coagulant and the anti-cardiolipins*** imply an associated autoimmune disorder, and you can expect a high ANA or other positive autoimmune serology. ***Factor V Leiden and prothrombin 20201G mutation*** are altered genes making them pathological roots of the altered coagulation balance, and immutable evidence of pathology. Furthermore, these genes confirm a breeder disorder for cvd-ctd's.

Laboratory tests for the hypercoagulable disorders can be grouped into several categories, as follows (with example elements of each set). Below that is a table with greater information on select tests. (Note that normal values may vary from one laboratory to the next.)

1 -	Direct indicators of active thrombosis		fibrinogen, d-dimer, fdp-fsp, plasminogen, t-at complex
2 -	Reflex or indirect markers of thrombosis		prot C, prot S, AT-3.
3 -	Pro-thrombotic species,	thrombophilic	prot C, prot S, at-3, f.VIII, apc-r, thrombin generation
		immune	apl: anticardiolipin, lupus anticoagulant, anti: beta-2-glypr, anca, mpo, pr-3
		metabolic	homocysteine, MTHFR
		rheological et al	SPEP / SIFE, PF4, Hgb, cryoglobulins, cryofibrinogen
4 -	Immutable root causes		factor-V.Leiden (R506Q), prothrombin mut. (20210G), MTHFR

Table of Select Hypercoagulable Tests and Their Interpretation

This table includes common and representative species with interpretation notes relevant to the assessment of hypercoagulable states.
It is not by any means a comprehensive table of all available coagulation tests nor does it interpret values for other clinical situations.
Some items can also cause hypocoagulability, but Interpretation Notes look mainly at the hypercoagulable related considerations.
Interpretation notes comment on high and low variances as pertains to hypercoagulability, some items relevant in both states.
The notes comment on causes of high and low variances, and (*italicized) physiological and clinical implications of that state.*
Some items are listed twice as they fit two categories or have variable implications depending on high versus low values.
Assay type denotes if a test measures concentration or activity of a chemical species, e.g. fibrinogen or d-dimer level,
- versus - aggregate function of a chemical system, pathway, or interaction, e.g. prothrombin time or APC resistance.
"Second tier" are rarer hypercoagulable items ordered only for strong suspicion after negative primary workup.
Second tier can also imply a reflex study, the further characterization of altered function or activity assays.
Normal values listed are typical, but details vary between labs. Check your own lab's reference ranges.
Abnormal values can represent either a cause of the coagulopathic state or reflex adjustments to it.

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

protein C	•		activity	Anticoagulant, thrombosis when low. (Consumption & DIC, liver dx, misc.) *Deficiency is strongly prothrombotic.*	*As above, when high, it is a reflex marker of hypercoagulability.*	Low C, S, AT3 mean no brakes on clotting. (Warfarin also causes low C, but there is a reason pt. is on it.)
protein S	•		antigen	Prot. C cofactor, endogenous anti-coagulant. (Congenital & acquired.) *Deficiency is strongly prothrombotic.*	*As above, when high, it is a reflex marker of hypercoagulability.*	For C, S, AT3, low functional assay can reflect low amount (antigen), dysfunctional version, or inhibition.
C4 binding protein (C4B)	•		305 - 695 mg/l		Acute phase, immune-inflamm., misc. *Reduces free prot S, thus thrombotic.*	Complement binding protein with high affinity for prot S. 2nd tier test.
antithrombin III	•		activity: 80 – 120 % antigen: 19 – 30 mg/dl	Anticoagulant, thrombosis when low. (Congenital defic., liver dx, misc.) *Deficiency is strongly prothrombotic.*	*As above, when high, it is a reflex marker of hypercoagulability.*	For C, S, AT3, dual nature: Low = potent cause of thrombosis. High = reflex marker of thrombosis.
dysfibrinogenemia	•		: activity/antigen > 0.7. : nl TT, aPTT, rept T. : or spec. gene mut.	Genetic or acq. (liver dx and misc). Low function mostly hypocoag., but *10-20% of subjects hypercoagulable.*	Thrombin time, aPTT, and reptilase time rapid in hypercoag versions. *Clot from high level or high func. act.*	Mix of causes. Blood can be normal, hypo-, or hypercoag. 2nd tier test.
plasminogen	•		65 – 120%	Low reflects consumption (marker), *AND absence propagates thrombus.*	Reflex elev. in thrombotic states. Listed above as thromb. marker.	Low = mark & cause of thrombosis. High = marker of thrombosis.
tissue plasminogen activator (tPA)	•		< 13 ng/mL activity: mixed methods	Activity often low with high antigen, from bound PAI-1. *Causes thrombosis.*	Released from abn. vessels & flow. *High antigen marker of clotting risk.*	Complex crucial relation to PAI-1. Thrombosis, low=cause, high=marker.
plasminogen activator inhibitor-1 (PAI-1)		•	4 – 43 ng/mL		Acute phase, trauma, sepsis, mi, misc. *Fibrinolysis decr., A & V thrombi, MI.*	Highly correlated, thrombic states & risk, high MI risk. Cause & marker.
plasminogen act. inh.-1 (PAI-1) 4G/5G		•	negative		4G allele gene mutation. *Augments & increases effects & risks of PAI-1.*	Assoc. with & raises coag. risks for other gene mut's. (V.Leiden, prot S.)
New and future tests	•	•				Expect ever increasing catalog of hypercoagulable species, gene mutations, and functional assays.
3b – Pro-thrombotic species, immune				Direct agents of excess thrombosis: antibodies active against thrombotic system components and inhibitors. *They: unbalance the system favoring clots; indicate autoimmunity, often reflecting another 1° hypercoag disorder.*		
antiphospholipid ab's			negative	*[Class of autoimmune antibodies. Assay by individual species listed next.]*	Autoimmune, inflammation, misc dx. *Procoagulants, hypercoagulable.*	Clotting by binding coag inhibitors, cell membrane & plt disruption, et al.
apl: anticardiolipin ab (ACA's: IgG, IgM, IgA)	•		< 12 neg. 12 - 20 indeterm.		Autoimmune, inflammation, misc dx. *Potent pro-thrombotic, basis of APLS.*	Ab's vs. mitochondrial membranes. Thrombotic effects throughout body.
anti beta-2-glycoprotein (anti apolipoprotein H)	•		< 20 u		Anticardiolipin subtype & cofactor. *Most potent & specific vector of APLS.*	Use ACA to screen APLS; B2GP/APPH to confirm if clinical diagnosis vague.
apl: lupus anticoagulant (LA, or LAC)	•		negative		Autoimmune, inflammation, misc dx. *Presence thrombotic, a vector of APLS.*	In vivo clots ("anticoag" name from in vitro effects). Lab assay is dRVVT.
dilute Russell viper venom time (dRVVT)		•	screen: < 45 sec mixing: corrected		Misc causes of long dRVVT, mixing study confirms LA. *Thrombotic, APLS.*	"Lupus AC" is an APLA class revealed indirectly with dRVV functional assay.
apl: anti prothrombin ab	•		IgG < 20 u		Anti-PL ab, analogous to beta-2-GP. *Presence thrombotic, a vector of APLS.*	Beta-2-GP is main element of ACA's. Anti-PT ab is main element of LAC.
apl: phosphatidylserine (anti PS ab: IgG, M, A)	•		< 20 neg. 20 - 30 indeterm.		Ab's vs. PS-prothrombin complex. *Presence thrombotic, a vector of APLS.*	APLA = Ab's vs PL-protein complex: aCL-B2GP = ACA; aPS-aPT = LAC.
apl: anti-phosphatidyl-ethanolamine, inositol, choline, glycerol, acid	•		< 10 u		Other phosphatidic acid derived anti-phospholipid ab's. *Vectors of APLS, mixed thrombogenicity.*	P-serine known thrombotic. Others likely, but lab relevance is mainly to infertility-abortion aspects of APLS.
ANCA: anti neutrophilic cytoplasmic antibodies c-anca = anti-proteinase-3 p-anca = anti-myeloperoxidase	•		< 1:20 or negative		Rise with immune vasculitis. Marker of inflamm. & thrombogenic vessels. *ANCA's can also cause clots, similar to APLA's, risk high when disease active.*	Vasculitic vessels are thrombogenic, even when plasma is not inherently thrombophilic. So, ANCA's mark risk, but they also have clotting effects.
3c – Pro-thrombotic species, metabolic				Agents of excess thrombosis: primary non-plasma metabolic-chemical factors with secondary effects on blood. *They indicate risk of prothrombotic state of the blood caused by altered chemistry not intrinsic to clotting path.*		
homocysteine	•		< 15 umol/l		Misc. genetic and metabolic causes. *Athero-occlusive vasc. dx, thrombosis.*	Causes vascular & endothelial injury, vessels thrombogenic; other effects.
MTHFR mutation C677T methylene tetrahydrofolate reductase	•		normal non hetero- or homozygous		Effects via homocysteine metabolism. *Thrombosis risk as for hyper-homocyst.*	Slows homocyst. conv. to methionine, raising level. Fetal, neuro risks, et al.
lipoprotein (a) (LP-a)	•		< 75 nmol/l		Bioactivity analogous to plasminogen. *Thrombic by plasma, plt, vasc. effects.*	Highly atherogenic, but clotting is also by inherent hypercoagulability.
PNH - flow cytometry paroxysmal nocturnal hemoglobinuria		•	FLAER CD55, CD59	Defic. of cell surf. prot. anchors (GPI). *Hemolysis, very high thrombosis risk.*	*GPI = glycosylphosphosphatidylinositol, cell membr. anchor for protective proteins.*	Absent GPI's, CD55 & 59 cannot protect cells from complement lysis.
3d – Pro-thrombotic species, rheological et al				Causes of intravascular thrombosis due to altered viscosity, aggregates, cells and platelets, and blood vessels. *They indicate risk of thrombosis from altered blood flow mechanics, due to formed elements or abnormal vessels.*		
heparin-PF4 Ab (HIPA) heparin - platelet factor 4 : IgG Heparin induced platelet antibody (HIT / HITT) Heparin induced thrombocytopenia II	•		OD < 0.400 (positive = OD > 0.4 with heparin inhibition > 50%)		HITT (HIT with thrombosis) caused by antibodies against heparin-PF4 complex. *High thrombogenicity via heparin inactivation & plt activation.*	Heparin-PF4 Ab ELISA is a screen for HITT, sensitive but not specific. Diagnosis resolved by doing SRA or HIPAA assay (see next).
serotonin release assay (SRA) (HIT/HITT)		•	< 20%		Despite thrombocytopenia from hep. induced ab's, *HIT is highly thrombotic.*	Detects HIT antibodies by platelet serotonin release. Specific for HIT.

heparin-induced platelet aggregation (HIPA/HIPAA)		•	< 30%		Distinguish true HIT from other low platelets by PF4-ELISA, SRA, HIPAA.	Like SRA, a function assay. Hep-PF4 IgG screens HIT, SRA-HIPAA confirm.
von Willebrand factor (vWF)	•		activity: 50 – 150 % antigen: 50 – 150 %	*Deficiency. causes hemorrhagic von Willebrand's disease. (See above.)*	Platelet adhesion-aggregat'n effects. *Thrombosis in misc clinical situations.*	vWF is multi-mode thrombotic, part clotting, part plt, vessel, rheol. effects.
von Willebrand factor protease (ADAMTS-13)	•		Activity 68 - 163 % Inhibitor < 0.4	Acq., imm., genetic (rare). *Cause of TTP thrombotic thrombocytopenia.*	*Low ADAMTS13 causes high levels vWF, thus diffuse platelet activation.*	ADMATS13 defic. or inhib. activates plt., with microthrombi & angiopathy.
cryoglobulins	•		negative		Immune, infect., cancer, misc. *Clots from viscosity, precipitates, 2° vasculitis.*	Multifactorial vector of thrombosis. Syndromic features allow clinical id.
cryofibrinogen	•		negative		Similar to cryoglob. but less common. *Vasculitis and thrombosis risk high.*	Large vessel thrombosis 25-40% of cases. Workup required for 1° cause.
gamma & clonal screen SPEP SIFE		•	normal profile, no gamma or else no M-spike		Para- & dysproteinemias, mainly Ig's, non-plasma hyperviscosity, Ig effects. *Resulting vascular stasis risks clotting.*	The proteins are not thrombic, but with their causes, often malign't, risk clots by viscous & particle rheology.
blood, serum viscosity		•	1.5 - 1.9 (relative to H2O)		Comparable to comments re SPEP. *Misc. dx e.g. Waldenstrom, myeloma.*	Hyperviscosity has many effects. Clot risks are relatively low but real.
hemoglobinopathies & erythroid pathologies	•		nl smear, hemogram, misc tests dx specific	*e.g., thalassemia, sickle cell disease, polycythemia, hemolytic anemias.*	Not all, but most red cell dyscrasias at risk. *Thrombosis high with some.*	Multi-mode clotting: coag-plasma, plt, rheol, immune, biochem effects.
myelo, leuko, thrombo, formed elem. cythemias	•		nl smear, hemogram, marrow, spep-sife, etc.	*Leukemias, thrombocytosis, MPD's myeloma & plasma dyscrasias, MGUS.*	Like red cell dx, thrombic risk variable but real. *Thrombosis high with some.*	Particle mechanics relevant, but also immune & membrane chem. effects.
parathormone	•		15 - 65 pg/ml		Micro-calcific medial arteriosclerosis. *Skin infarcts from thrombic vessels.*	Mostly renal hyperparathyroidism, 2° or 3° (misnomered "calciphylaxis").
4 – Immutable root causes				Thrombotic species, prime or cofactor, all repeats of above, listed again as they are genes, roots in the system. *As genes, immutable origins of pathology from which 2° changes derive. Expect ever more available from labs.*		
prothrombin 20210G	•		normal	*(See above.)*	*Prothrombin elevated, promotes clot.*	Relatively frequent cause of clots.
prothrombin 19911A	•		normal	*(See above.)*	*Thrombic risk, not as much as 20210.*	Example, expanding catalog of items.
MTHFR C677T	•		normal	*(See above.)*	*Clot risk due to homocysteine metab.*	Clotting is one among many risks.
factor V Leiden R506Q	•		normal	*(See above.)*	*Resists APC, uninhib'd. Clot risk high.*	Frequent & high risk cause of clots.
factor V HR2 allele	•		normal	*(See above.)*	Coinherited with fV.Leid. raises risk.	Example, expanding catalog of items.
plasm'gen PAI-1 4G/5G	•		normal	*(See above.)*	*Raises PAI-1 activity, promotes clot.*	Augments risks for other coag species.
5 – General & non-thrombotic				General laboratory studies that are part of the evaluation of hypercoagulable disorders and states. *These are not thrombotic elements or species, rather markers of underlying, causative, or associated diseases.*		
CBC, hemogram	•		rbc, wbc, plts, diff, morphology		Polycythemia, thrombocytosis, leuko-cytoses, eos, red cell disorders, etc.	Reveals inflamm., micro-occl. dx and non-hypercoag hematopathologies.
CMP, U/A	•		blood chemistry, urinalysis		Liver, renal disease, etc. that might imply coagulopathy assoc. disease.	Such dx likely known by hx or exam, but useful for 1st eval or track status.
autoimmune screen ANA, ANA w/reflex	•		negative		Std. tests. Crucial to hypercoag eval due to close coag-immune affiliation.	Eval auto-immunity & chronic inflamm. *Assess thrombosis, cause vs reaction.*
autoimmune testing individual antibodies	•		negative		If ANA is neg, test individual ab's, e.g. dsDNA, SSA-B, RNP, CCP, Sm, Jo, etc.	Std ANA useful if positive, and reflex or specific ab testing identifies dx.
inflammation screen sed rate, crp, ldh	•				Standard tests and ranges.	Generic indicators of inflammation. *Assess thrombosis, cause vs reaction.*
inflammation screen complement	•			Std tests & ranges. *(Relevant values high or low, specific for each item.)*	Standard tests and ranges.	Specific path marker of inflammation. *Assess thrombosis, cause vs reaction.*
general tumor markers, CEA, AFP, et al.	•		normal, low, neg.	*Carcinoembryonic antigen, alpha fetoprotein, etc.*	Not thrombotic per se; presence implies cancer as cause of clots.	Useful if cause of clot elusive and workup seeks non-blood disorders.
CXR, CT, US, et al	•		normal, negative	*Imaging of chest, abdomen, pelvis.*	Show tumor or other dx causing clot.	Adjunct / followup to pos. CEA, etc.
miscellaneous (tests for specific organs or diseases)	•			Specific to diagnosis or differential being worked up.	Specific to diagnosis or differential being worked up.	Tests to evaluate cause of coagulo-pathic state or associated disease, e.g., HLA-B51 for Behçet's, serology for immune thyroid or bowel dx.
6 – Non-chemistry				Non-blood non-chemistry lab tests, or technological exams that elucidate status of blood flow and circulation. *Confirm & measure effects of thrombosis, low flow & hypoxia; eval macro-vascular vs. micro-occlusive ischemia.*		
tcpO2 (trans-cutaneous pO2)			60 – 100 mm Hg	Low = hypoxia from inadequate flow. *Often 0-10 around micro-occl. ulcers. Guides rx, e.g. warfarin or hyperbar.*	*Also test normal skin outside of the target lesion (e.g. ulcer), to confirm difference of low vs normal O2.*	Shows hypoxia but not cause. Use with doppler pressures to assess macro vs. micro dx and treatment.
arterial dopplers, segmental pressures, & brachial indexes			thigh thbi > 1.0 ankle abi > 0.9 toe tbi > 0.7	Low = large vessel atherosclerosis. *Indicates macrovascular ischemia.*	Normal = large vessel bulk flow good. *No macrovascular ischemia.*	Use abi's as adjunct to tcpO2's : Low = non-coag cause of ischemia. Nl = low tcpO2's due to micro-occlu.
laser doppler flow (LDF)			relative units *(device-mfg specific)*	Low = low blood flow. *Measures flow in micro-circulation, but does not distinguish macro vs micro causes.*	Normal = small vessel flow & tissue perfusion are good. *No ischemia.*	Utility of LDF (flow) comparable to tcpO2 (oxygen). Use doppler-abi's to elucidate macro vs micro dx.
spectral imaging			low flow *(device-tech specific)*	2D planar video-dynamic mapping and dye imaging of flow patterns.	Normal = small vessel flow & tissue perfusion are good. *No ischemia.*	Info. similar to tcpO2 & LDF, plus timewise dynamics (various devices).
histology (tissue biopsy)			normal cells & tissue architecture	Observe: 1 - clot causes: acute & chron. vasculitis, micro-angiopathy; 3 - late effects: vasc. fibro-stenosis.	Obs: 2 - clots & early effects: acute & micro thrombi, cell necrosis, min. inflam., organization, recanalization.	Blood tests, and TcpO2 & vascular studies are inferential. Histology is direct visual evidence of clotting.

Since circa 1990-1995, there have been ever increasing laboratory tests to assess pro-thrombotic blood chemistry, offered by commercial and clinical labs. As awareness of the hypercoagulable disorders has slowly increased, and as more tests come online in clinical use, the interest in doing relevant laboratory workup has increased, but with so many tests that might be ordered, so has the mystery and confusion. In response, many labs now offer "panels" of tests, select sets of individual assays that are most apropos of a given clinical condition. No panel by itself is comprehensive, but they can be a convenient starting point to work up the diagnosis in a patient suspected of having a hypercoagulable condition. These include items such as "thrombosis panel", "thrombophilia screen", "thrombophilia mutation analysis", "thrombotic marker panel", "fibrinolysis panel", "thrombosis, venous risk profile", "thrombotic risk profile", "markers of coagulation activation", "extrinsic pathway coagulation factor profile", "intrinsic pathway coagulation factor profile", "recurrent miscarriage panel", "recurrent miscarriage, fetal demise profile".

Note that many of the "thrombosis panels" and "thrombophilia screens" offered by clinical labs, while very useful and convenient, are the same collection of tests that were included as far back as circa 2005-2010. In the ensuing 10-15 years, many new prothrombotic species have been identified, and a systematic understanding of hypercoagulability has increased. The panels suggested below will not seem to correlate with many of the standard commercial panels, and this reflects the abundance of new information that has been gained in this interval.

Some tests will be ordered to confirm an almost certain clinical diagnosis. For example, heparin induced thrombocytopenia (HIT), hyperparathyroidism, or paroxysmal nocturnal hemoglobinuria (PNH), might be correct based on history, physical exam, and general tests, but unequivocal validation by specific tests is still required. Others, such as the plasma based thrombophilic disorders will be suspected based on history, but there is no other certainty, and the tests are thus a bit less directed or certain to yield a positive result. Remember, "hypercoagulability" often has a vernacular connotation of the plasma-thrombophilic and the autoimmune-antiphospholipid disorders, but hypercoagulability has broader implications. Recall Virchow's triad – thrombosis can result from (1) pathologies of the blood including but not exclusively due to the inherent thrombogenicity of the plasma, (2) pathologies of the vessels which make them thrombogenic even for normal blood and plasma, and (3) how blood and vessels interact via the dynamics of blood flow, even when blood and vessels are both intrinsically normal. The question is whether you are looking to make a diagnosis of something else not primarily of the thrombotic system, versus suspicion that the coagulation system itself is altered, or whether you are looking for a classical disease well known and long named, versus one of the newly appreciated hypercoagulable disorders.

Below are suggested working subsets of the above tests, a guide to the most pragmatic, efficient, and cost effective ways to assess hypercoagulable patients. These suggestions might vary from one practice to another. An obstetrician working up recurrent miscarriages or a doctor evaluating recurrent pulmonary thrombosis or emboli might rank the various tests differently than a doctor evaluating wounds and surgical complications. These variances can arise from the documented risk profiles and disease correlations that appertain to each condition. However, there is mostly commonality to all of these conditions. The reason for suggesting different subsets is that some of these tests are expensive. A comprehensive order that included all of the above would be obscenely expensive and simply not warranted for most patients in whom a valid diagnosis can be made with a just a few of them.

These suggested sets are based on criteria such as degree of suspicion of a hypercoagulable disorder, timeliness that information is needed, and cost. Expense may be important to some patients, and there is the practical issue of turnaround time. Some tests are performed in the clinical lab of many or most hospitals, results available in 24-48 hours, whereas others that must be sent out to reference labs often take two or three weeks to see the result. Workup done as an outpatient, ordered through the office for a chronic non-critical condition, is quite different than the information needed in a hospitalized patient with a serious complication that needs urgent diagnosis. In a patient for whom a hypercoagulable diagnosis is not strongly suspected but still needs to be ruled out, the simple screens that are useful are different than for a patient whom the clinical diagnosis is already certain but detailed lab testing is needed to identify species so that future risk can be assessed and treatment planned. Depending on which tests your own hospital or lab offers in house, some of the following items can be substituted for others with similar diagnostic relevance.

The following lab sets try to identify **(1)** if there is active thrombosis, or beyond that, **(2)** an active ***hypercoagulable state***, and then **(3)** if there is an underlying ***hypercoagulable disorder*** or risk. Remember, having a hypercoagulable disorder or predisposition does not necessarily mean that you are always in a hypercoagulable state. Likewise, being in a hypercoagulable state can be a transient imbalance not necessarily due to an inherent hypercoagulable species. Panels:
1 – Signs of active or recent ***thrombosis*** are based on looking for direct evidence of clotting and thrombus (thrombin, fibrinogen, and derivatives).
2 – Signs of a thrombotic or hypercoagulable ***state*** look for reflex upregulation of endogenous anticoagulants or other thrombosis induced items.
3 – Signs of a thrombotic or hypercoagulable ***disorder***, risk, or predisposition are based on finding § prothrombotic species (abnormal clotting proteins or genes, other hypercoagulable chemicals), § presence of immune or inflammatory procoagulants, or reflex changes such as secondary autoimmunization, § prothrombotic alterations of blood rheology or vessels, or § consequences of thrombosis resulting in impaired circulation.

Test	Variance from nl		Interpretation	Notes
	Low	High		
Panel 1-a	**Quick screen for thrombosis**		**Simple screen to identify active thrombosis.** It implies a possible hypercoagulable ***state*** (chronic or sustained) but does not confirm. It does not identify category or species of a primary hypercoag ***disorder***, not even that there is one. *It is not relevant if there is active trauma, bleeding, known large thrombus, other obvious or acute events.*	
fibrinogen	•	•	Low due to consumption. High in hypercoagulable states.	Panel best used to identify disorders where thrombosis is suspected but not overt. **Fibrinogen & d-dimer** are inexpensive, performed by most hospital labs, **TAT** the opposite but sensitive. **PT-frags, & f.mono.** more sensitive than **fdp**, but not offered in small labs; the 3 are comparable, need only one for diagnosis. **Biopsy** gives high quality info – do not miss opportunity if safe to do.
d-dimer, or other fdp		•	Degrade products imply thrombus present, prior-recent.	
TAT complex		•	Sign thrombin generation, implies active-current thrombosis.	
prothrombin fragment 1, 2		•	*Indicates thrombin conversion, implies active thrombosis.*	
fibrin monomer		•	*Indicates active thrombin-fibrinogen, implies thrombosis.*	
			Order fibr'gen, d-dimer, & one from among the other 3.	
histology (tissue biopsy)			Direct visualization of old and new thrombus, & 2° effects.	

Panel 1-b	**Full screen for thrombosis**		**Thorough screen to identify active thrombosis.** Full Panel 1a plus the two items here (if offered by lab). These are all direct residues of thrombin and fibrin except nETP which is an indirect but potent indicator of thrombic potential.	
fibrinopeptide A		•	*Indicates fibrin conversion, implies thrombosis.*	Costly, but sensitive when diagnosis remains elusive. **FpA** similar to TAT et al, but few labs offer. **nETP** valuable for diagnosis & prognosis, but rarely offered.
thrombin generation (nETP)		•	*Indirect measure, marker of capacity to make thrombus.*	
			2nd tier. Order all 5 items from Panel 1a, plus these 2.	
Panel 2-a	**Quick screen for hypercoag state**		**Simple screen to identify a hypercoagulable state.** This implies not just signs of active or recent thrombosis, but evidence of heightened thrombic potential or of longer term compensatory adjustments to persistent coagulation. It tends to confirm a hypercoagulable ***state***, but it does not identify the underlying primary hypercoagulable ***disorder***.	
Panel 1-a			Fibrinogen, d-dimer, & TAT (or PT-frags or f-monomer).	**Panel 1** identifies that thrombosis has or is occurring. **Panel 2** identifies that coagulation has been chronic or ongoing, or that blood is in a hyperthrombotic state. **C**, **S**, & **AT-3** do not vary synchronously, so check all three for better diagnostic sensitivity. Plasminogen activator and inhibitor also useful but not as first line screen. **Bleeding time** easy, direct on the patient, meaningful if very rapid.
protein C		•	Endogenous anticoagulants, similar interpretation for all. Low causes thrombosis. **High** = upregulation in response to ongoing thrombosis, markers of hypercoagulable state.	
protein S		•		
antithrombin III		•		
plasminogen		•	Rises in thrombotic states, marker of ongoing thrombosis.	
bleeding time	•		Directly observe clotting rate, rapid implies hypercoag.	
			Order Panel 1-a and C, S, & AT-3, plasminogen.	
Panel 2-b	**Full screen for hypercoag state**		**Thorough screen to identify a hypercoagulable state.** Full Panel 1b & 2a plus the additional items here. The extra items have varied physiologies and can cause thrombosis, but all are markers of heightened ongoing thrombotic risk.	
Panel 1-a, b			Fibrinogen, d-dimer, TAT, PT-frags, f-mono, *f-peptide-A*.	Other than nETP, the additional items on this panel are generally available from reference labs. **Panel 1** identifies occurrence of thrombus. Readily available **Panel 2a** can identify a hypercoag state. **Panel 2b** tests additional species, thrombotic and vascular (ANCA's), for a more sensitive or thorough indication of heightened risk or sustained state of thrombosis, at macro or micro scales.
Panel 2-a			Protein C, protein S, antithrombin-3, plasminogen.	
tiss. plasminogen act'r (tPA)	•	•	Low causes clot. High = marker of hypercoag conditions.	
plasminogen act-inh (PAI-1)		•	High causes clot, & reflex marker of hypercoag conditions.	
ANCA's anti-PR-3, anti-MPO		•	Causes clots, but also indicate heightened thrombic state.	
thrombin generation (nETP)		•	Marker, capacity to make thrombus, high in hypercoag state.	
			Order Panels 1-b, 2-a, and tPA, PAI-1, ANCA's, & nETP.	
Panel 3-a	**Hypercoag scrn, thrombophilic dis.**		**Panel of tests to identify primary causes & hypercoag species, focus on the plasma coagulation system.** This panel derives from assay group 3a (thrombophilics), some of which are uncommon or less relevant. Listed here are the main items, balancing diagnostic & economic efficiency. For more precision, the others can be ordered as 2nd tier tests.	
factor VIII		•	Potent primary instigator of thrombosis. High causes clot.	High yield first tier test, readily available in clinical labs.
von Willebrand factor (vWF)		•	Potent thrombogen by f.VIII promotion et al. High = clot.	Not as freq., but 1st tier for potent effect & common test.
prothrombin mut. (20210G)		•	Hetero- or homozygous mutation = high thrombosis risk.	Both gene tests identify common root causes of clotting. Both are "send out" tests easily ordered, 2-3 wk reporting.
factor V Leiden (R506Q)		•	Hetero- or homozygous mutation = high thrombosis risk.	
activ. prot. C resist. (APCR)	•		Low value means that f.V resists protein C, promoting clot.	Test for f.V Leiden: indirect but readily available and quick.
protein C	•	•	Endogenous anticoagulants, similar interpretation for all. High values reflect a thrombotic state. **Low** = accelerated thrombin conversion, potent causes of thrombosis.	**C**, **S**, & **AT-3**, listed in Panel 2 as hypercoag markers, are also potent thrombogens when low. Frequent. Not in synch, so order all three. The tests are readily available.
protein S	•	•		
antithrombin III	•	•		
plasminogen	•	•	Low allows thrombus extension, (low & high mark clotting).	These 3 identify thrombosis from weak clot degradation, and offer multi insights into coagulation state. **Plasm'gen** test readily available, **tPA** & **PAI-1** unlikely in smaller labs.
tiss. plasm'gn activator (tPA)	•	•	Low activity equiv. to low plasminogen, propagates clot.	
plasminogen act-inh (PAI-1)		•	High implies low tPA activity impl. low plasmin impl. clot.	
			For quick workup, ignore gene tests and order APCR. For high yield, quick turnaround panel offered in all labs: **F.VIII, vWF, APCR, protC, protS, AT-3, plasminogen.**	**Panels 1, 2** identified hypercoag state, or do concurrently. For slower but more thorough diagnostic precision, order all items. Order 2nd tier tests if diagnosis remains elusive.
Second tier			*factor IX (hypercoagulable when high) • factor XI (high) • dysfibrinogenemia (rapid) • C4 binding protein (C4B, high)*	
Panel 3-b	**Hypercoag scrn, autoimmune dis.**		**Panel of tests to identify primary causes & hypercoag species, focus on immune procoagulants.** This panel derives from assay group 3b (immune), most relevant to a primary hypercoag workup. The few not listed here can be ordered as 2nd tier tests. Practical subsets for efficient screening are listed in the comprehensive or integrated panels below.	
ANA, w/reflex		•	ANA's mark the cvd-ctd's, generic ANA or misc subtypes.	Identify autoimm. state or dx (some cvd-ctd pts sero-neg).
inflam. screen: esr, crp, ldh		•	Non-specific markers, acute inflammation (& misc others).	Moot if infl. obvious. Useful for occult dx or track therapy.
inflam. screen: complement		•	Variable specificity, acute & chronic inflammation, misc dx.	Can be useful for immune & occult disorders with clot risk.
antiphospholipid antibodies		•	Basis of hypercoag APLA synd., often assoc. with immune dx.	Some labs use APL panels in lieu of ordering indiv. items.
anti cardiolipin antibodies		•	APLAS vector, thrombosis risk high when present.	Order all IgG,A,M. Generally available, good APLA screen.
anti beta-2-glycoprotein		•	Most potent & specific APLAS vector, variant of ACA's.	More specific test for ACA/APLA, but not always offered.
lupus anticoagulant (LA, LAC)		•	The other main group of APLA's, high thrombosis risk.	Available. Order both LA & ACA for complete dx of APLA.
dil. Russell viper ven. tm. (dRVVT)		•	This is not a species, just a test, the test for lupus-AC.	LAC often ordered as or reported as dRVVT.
anti prothrombin ab (aPT)		•	APLAS vector, clotting when high, specific element of LAC.	B2GP is main ACA; similarly aPT is main LAC element, & aPS (2nd tier) similar. Order all for full dx APLA; not in many labs.
anti phosphatidylserine ab		•	APLAS vector, similar to aPT, a species of the lupus-AC.	
anti neutro. cyto. ab (ANCA)		•	High = marker and also cause of thrombosis, similar to APLA.	ANCA's reflect vasculitis & hypercoag state, and they raise thrombic risk, thus useful to eval various immune, inflamm., & thrombic states. Order panel or itemized, specific to lab.
anti-proteinase-3 (c-anca)		•	C-ANCA is older term for what is now recognized as AP3.	
anti-myeloperoxidase (p-anca)		•	P-ANCA is older term for what is now recognized as MPO.	
			For quick inexpensive **basic screen**, order **ANA**, **ACA**, **LAC**.	For **thorough** 1st tier testing, add **B2GP**, **aPT**, **ANCA**.

Panel 3-c	**Hypercoag scrn, other disorders**		**Panel of tests to identify primary causes & hypercoag species, focus on metabolic and rheological items.** This derives from assays 3c-d, a mixed group with variable hypercoag potencies. Listed here are key items balancing diagnostic & economic efficiency. Others can be ordered as 2nd tier tests. Practical diagnostic subsets are listed below.	
homocysteine		•	High values risk atherosclerotic vascular dx & thrombosis.	Easily ordered, on many basic hypercoagulable panels.
MTHFR mutation C677T		•	Presence of mutation risks thrombosis, via homocysteine.	F.V Leiden etc. more potent, but useful if 1° workup neg.
lipoprotein (a) (LP-a)		•	High = thrombic via effects on plasma, platelets, & vessels.	Usually part of coronary vascular eval, 2nd tier for clotting.
PNH - flow cytometry	•		Low cell surface GPI causes hemolysis & high clot risk.	2nd tier. No value ordering absent clinical features PNH.
heparin-PF4 Ab (HIPA)		•	Positive antibodies imply thrombic HITT (but not confirm).	Hep-PF4 ab screens HIT/HITT, available in most hospital labs. SRA & HIPAA confirm plt effects, risks for thr'penia & thrombosis; not so available. Irrelevant if HIT not suspect.
serotonin release assay (SRA)		•	High value confirms presence of thrombic heparin ab's.	
hep. induc. plt. aggr. assay (HIPAA)		•	High value confirms presence of thrombic heparin ab's.	
von Willebrand factor (vWF)		•	High = thrombic via f.VIII (above), also by plt & vasc effects.	Broad & potent effects make this 1st tier, test common.
vWF protease (ADAMTS-13)	•		Low = increased vWF = diffuse plt activation = thrombic.	A-13 not widely offered, 2nd tier only, especially if vWF nl.
cryoglobulins		•	Presence = thrombogenic (viscosity, precipitates, vasculitis).	If present, workup req'd for primary or assoc. dx. Being similar, **rheumatoid factor** can substitute for cryoglobulin.
cryofibrinogen		•	Presence = thrombogenic (high risk thrombosis & vasculitis).	
SPEP, SIFE, gamma		•	Paraproteins imply thrombogenicity from underlying disease.	Screen with SPEP. Workup to make primary diagnosis.
serum viscosity		•	Elevated = same implications as cryo- & paraproteinemias.	2nd tier, not needed if cause of viscosity already found.
cbc-diff, hemoglobin studies			Variances that risk clot specific for red cell dx in question.	Common tests, relevant to thrombic workup based on details of history, exam, & working differential diagnosis.
platelet studies, marrow bx			Variances that risk clot specific for each plt & myeloid dx.	
parathormone		•	Elev. = hyper-pth, thromb. relevant in select clinical states.	2nd tier. Not relevant absent typical skin infarcts & ulcers.
CEA, AFP, tumor markers		•	Presence or high suggests occult tumor & Trousseau synd.	Common test, considered by some mandatory for w/u dvt.
CXR, CT, US, other imaging			Can reveal tumor or other pathology causing errant clots.	Readily done, specific studies based on clinical profile.
			Heterogen. disorders with secondary coag effects. Order tests selectively based on clinical suspicions. Screen with 1st tier tests, then 2nd tier if diagnosis remains elusive.	For general hypercoag workup without suspicion of a specific diagnosis, screen with **homocysteine**, **HIPA**, **vWF**, **cryoglobulin**, **cryofibrinogen**, (or **rheum.f.**), **SPEP**.

Panel 3-d	**Non-chemistry, adjunct studies**		**Physical tests, items other than clinical hematology and chemistry.** These tests demonstrate the physical presence or functional consequences of thrombosis and resulting altered blood flow or ischemia. They reveal vascular insufficiency of any cause, which in conjunction with clinical profile can identify and quantify effects of thrombosis.	
tcpO2 (trans-cutaneous pO2)	•		Low = hypoxia, reduced flow; functional assay of circulation.	TcpO2's are at all hyperbaric facilities, simple bedside test. Use tcpO2 with abi's to resolve macro vs. micro occlusion.
art. doppler, brachial index	•		Low = reduced macrovascular blood pressure & flow.	
laser doppler flow (LDF)	•		Low = hypoxia, reduced flow; functional assay of circulation.	LDF (flow) & tcpO2 (flux) give similar info, no need for both.
histology (tissue biopsy)			Directly observe microthrombi, causes, & consequences.	Essential tool in hypercoag dx, from debridement or biopsy.
			TcpO2 & biopsy-**histology** yield high value confirmatory information. Always do them when safe or feasible.	Whether TcpO2 or substitute (LDF, spectral), combine with ABI's for robust concept of where flows are altered.

The panels above suggest a systematic way to evaluate categories of hypercoagulability, giving priority to the most common or prevalent species and the cheapest or most available tests (but also listing less likely second tier tests to be ordered when diagnosis remains elusive). The following panels are the pragmatic choices, actual working order sets that can be prescribed to work up conditions of suspected hypercoagulability. These are generic or broad spectrum screens of general hypercoagulability (whereas targeted workup for defined clinical profiles such as fetal demise or familial venous thromboembolism or suspected myeloma might be more refined or more inclusive of select second tier tests). There are 4 panels:
a – A quick general purpose screen using tests available in nearly all hospital labs, relatively inexpensive, with rapid turnaround or reporting times.
b – A robust screen, much more detailed. It is costlier & slower to report, but also most likely to pick up majority of hypercoagulable diagnoses.
c – A comprehensive screen, full spectrum of first tier and certain second tier tests, suitable for elusive diagnoses or refractory thrombotic states.
d – A maintenance screen that can be used to track status or flareup of disease or adequacy of treatment.

Panel 4-a	**Mixed panel, quick screen**			**General purpose simple screen.** This is likely to identify a hypercoagulable state and some of the prevalent causes. It uses common tests available in most hospital labs, inexpensive, usually with rapid results. It might not identify the primary abnormality, but it will confirm a thrombotic state, with some sense if plasma protein versus immune in origin. a = thrombosis marker; b = hypercoagulable state; c = plasma species; d = immune species; f = anatomy & functional.	
fibrinogen	a	•	•	Low = clot & consumption. High = freq. hypercoag marker.	Common pathway and finding in many hypercoag states.
d-dimer, or other fdp	a		•	Fibrin degrade products imply prior or recent thrombosis.	Often rise if thrombosis has occurred.
TAT complex	a		•	Sign thrombin generation, implies active-current thrombosis.	*Exclude if not offered by lab, or long turnaround time.*
protein C	bc	•	•	Endogenous anticoagulants, similar interpretation for all. Low = cause of thrombosis. High = marker of hypercoagulable state.	These three species are not in synch, so order all three.
protein S	bc	•	•		
antithrombin III	bc	•	•		
plasminogen	bc	•	•	Low = thrombotic. High = marker of ongoing thrombosis.	Same implications as C-S-AT3.
bleeding time	a	•		Directly observe clotting rate, rapid implies hypercoag.	Simple office or bedside test, or observation in surgery.
activated prot. C resistance	c	•		Low = factor V resists protein C, promoting clot.	This is a test for abnormal factor V, usually f. V Leiden.
factor VIII	c	•	•	High = thrombotic, potent primary instigator of clotting.	Also important low = hemophilia A, hypocoag & bleeding.
von Willebrand factor (vWF)	c	•	•	High = thrombotic, via f. VIII and other effects.	Also important when low, hypocoagulability and bleeding.
ANA, w/reflex	d		•	High = autoimmunity, cvd-ctd; immune hypercoag more apt.	If ANA positive, lab will "reflex" to specific auto-antibodies.
lupus anticoag. (or dRVVT)	d		•	High = high thrombosis risk; a main group of the APLA's.	Order both LA & ACA for complete screen of APLAS.
anti cardiolipin antibodies	d		•	High = high thrombosis risk; the other main APLAS vector.	Order all IgG,A,M. If available, can use beta-2-gp instead.
homocysteine	e		•	High risks atherosclerosis & thrombosis. Screen for MTHFR.	Easily ordered, on many basic hypercoagulable panels.
cbc, hemogram	f			Blood count variances reveal multiple possible problems.	
tcpO2 (trans-cutaneous pO2)	f	•		Low = hypoxia, low flow; parse macro-micro with doppler-abi's.	*Easy test, but only if available (else LDF or similar, if avail.).*
histology (tissue biopsy)	f			Direct observation of microthrombi & infarction.	*High yield diagnostic, relevant when debride-biopsy possible.*
				Order all simultaneously as practical first tier screen.	Most labs do all, thus efficient. Histo if safe, tcpO2 if avail.

Panel 4-b	**Mixed panel, robust screen**		**Robust diagnostic screen.** This group starts with Panel 4-a, then adds other tests that recognize a thrombotic state or cause. Due to expense, it is prudent to do Panel 4-a, review results, then order tests from this panel if results are inconclusive. However, on first round, order whatever is relevant if history and exam imply a specific diagnosis. a= thromb. mark; b= hypercoag state; c= plasma spp; d= immune spp; e= metabolic, rheologic; f= anatomy, functional.	
Include from **Panel 4-a** >>	a		**Fibrinogen, d-dimer or other fdp-fsp.**	
TAT complex	a	•	High = thrombin generation, sign of active thrombosis.	Not offered all labs. Similar info, so both not needed but preferred for elusive diagnosis. Insist on at least one.
prothrombin fragment 1, 2	a	•	High = thrombin conversion, indicates active thrombosis.	
fibrin monomer	a	•	High = fibrinogen conversion by thrombin, marker thrombosis.	More sensitive than fdp's. Not offered all labs. Similar info, both not needed, but insist on at least one.
fibrinopeptide A (FpA)	a	•	High = fibrin conversion, implies active thrombosis.	
thrombin generation (nETP)	ab	•	Marker, capacity to make thrombus, high in hypercoag state.	Sensitive marker thrombic potential, for diag. & prognosis.
Include from **Panel 4-a** >>	bc		**Plasminogen, prot.C, prot.S, antithromb-3, bleed time.**	
tiss. plasminogen act'r (tPA)	bc •	•	Low causes clot. High = marker of hypercoag conditions.	Not at all labs, but if available, can give insights to cause and status of hypercoag state and origin of thrombosis.
plasminogen act-inh (PAI-1)	bc	•	High causes clot, & reflex marker of hypercoag conditions.	
anti neutro. cyto. ab (ANCA)	bc	•	Causes clots, but also indicate heightened thrombic state.	Use to eval thrombic status & risk, also imm.-inflam. origins.
Include from **Panel 4-a** >>	c		**Factor VIII, von Willebrand (vWF), act. prot. C resistance.**	
prothrombin mut. (20210G)	c	•	Hetero- or homozygous mutation = high thrombosis risk.	Both gene tests identify common root causes of clotting. Both are "send out" tests easily ordered, 2-3 wk reporting.
factor V Leiden (R506Q)	c	•	Hetero- or homozygous mutation = high thrombosis risk.	
Include from **Panel 4-a** >>	d		**ANA w/reflex, lupus anticoagulant, anti cardiolipin ab.**	
anti-proteinase-3 (c-anca)	d	•	C-ANCA is older term for what is now recognized as AP3.	The specific forms for the ANCA's. They reflect vasculitis & hypercoagulable state, and they raise thrombotic risk.
anti-myeloperoxid. (p-anca)	d	•	P-ANCA is older term for what is now recognized as MPO.	
anti beta-2-glycoprotein	d	•	Most potent & specific APLAS vector, variant of ACA's.	B2GP is main ACA, specific test for anticardiolipins/APLAS.
anti prothrombin ab (aPT)	d	•	APLAS vector, clotting when high, specific element of LAC.	Similarly, aPT is main LAC element, more specific than LAC/dRVVT. aPS is similar to aPT, useful 2nd tier test.
anti phosphatidylserine ab	d	•	APLAS vector, similar to aPT, a species of the lupus-AC.	
inflam. scrn: esr, crp, ldh	d	•	Non-specific markers, acute inflammation (& misc others).	Moot if infl. obvious. Useful for occult dx or track therapy.
inflam. scrn: complement	d	•	Variable specificity, acute & chronic inflammation, misc dx.	Can be useful for immune & occult disorders with clot risk.
heparin-PF4 Ab (HIPA)	d	•	Positive antibodies imply thrombic HITT (but not confirm).	Screens for HIT/HITT, available in most hospital labs.
Include from **Panel 4-a** >>	ef		**Cbc-hemogram, tcpO2 / TCOM, histology.**	For elusive dx, histo more imperative, biopsy or debride.
MTHFR mutation C677T	e	•	Presence of mutation risks thrombosis, via homocysteine.	F.V Leiden etc. more potent, but useful if 1° workup neg.
cryoglobulins	e	•	Presence = thrombogenic (viscosity, precipitates, vasculitis).	If present, workup req'd for primary or assoc. dx. Being similar, **rheumatoid factor** can substitute for cryoglobulin.
cryofibrinogen	e	•	Presence = thrombogenic (high risk thrombosis & vasculitis).	
SPEP, SIFE, gamma	e	•	Paraproteins imply thrombogenicity from underlying disease.	Screen with SPEP. Workup to make primary diagnosis.
CEA, AFP	e	•	Presence or high suggests occult tumor & Trousseau synd.	Common test, considered by some mandatory for w/u dvt.
CMP, U/A	e		Can show metabolic or organ specific dx assoc. with clots.	Most apt to show liver or renal dx, 1° cause or 2° to clots.
Flow studies - laser, spectral	f		Can give detailed map of cutaneous or surface blood flow.	Use if tcpO2 not avail., but also useful as parallel study.
Radiographic imaging	f		Can reveal tumor or other pathology causing errant clots.	Be specific based on clinical profile and differential dx.
			Order all or order selectively based on clinical profile.	Many of these go to reference labs with long turnaround.
Panel 4-c	**Mixed panel, in depth eval.**		**Comprehensive screen.** It is unlikely to have done Panels 4-a and 4-b without arriving at a diagnosis if indeed a hypercoagulable state exists. However, if suspicion is high but workup negative, or workup is suggestive but more specificity is needed for certain disorders, then order these additional items. This panel is not a unified battery of tests. Select those which can clarify suspected specific disorders based on the working differential diagnosis.	
Misc tests from above			Items on Assay table & Panels-3 that are not on Panels-4.	Second tier tests when primary studies are equivocal.
lipoprotein (a) (LP-a)		•	High = thrombic via effects on plasma, platelets, & vessels.	Usually part of coronary vascular eval, 2nd tier for clotting.
PNH - flow cytometry	•		Low cell surface GPI causes hemolysis & high clot risk.	2nd tier. No value ordering absent clinical features PNH.
parathormone		•	Elev. = hyper-pth, thromb. relevant in select clinical states.	2nd tier. Not relevant absent typical skin infarcts & ulcers.
serum viscosity		•	Elevated = same implications as cryo- & paraproteinemias.	2nd tier, not needed if cause of viscosity already found.
hemoglobin studies		•	Variances that risk clot specific for red cell dx in question.	For diagnosis of sickle, thalassemia, etc..
bone marrow bx			Variances that risk clot specific for each plt & myeloid dx.	For diagnosis of formed element blood disorders.
others			Anything else relevant to a specific patient and diff. dx.	These look mainly for cause, not hypercoag state per se.
			Order selectively based on specific clinical profile.	Not needed if pt has no clinical hints of a particular dx.
Panel 4-d	**Followup and maintenance rx**		**Maintenance screen.** Like many disorders, hypercoagulability can be short term and transient, or quiet but with risk of instability, or chronic and active. Clinical surveillance is often needed to gauge the status of the hypercoagulable species or state or underlying cause. Ongoing necessity and duration of treatment must also be decided. This can be done with a limited subset of the above tests, some general markers plus those previously known to be altered.	
			Direct markers. (Panel 1-a, thrombosis screen.)	Identifies that thrombosis has or is occurring.
fibrinogen	•	•	Low due to consumption. High in hypercoagulable states.	To identify occult or subclinical states of active but non-overt micro thrombosis. If available, ***PT-frags, & fibrin monomer*** can also be done, more sensitive than fdp's.
d-dimer, or other fdp		•	Degrade products imply thrombus present, prior-recent.	
TAT complex		•	Sign thrombin generation, implies active-current thrombosis.	
			Reflex markers. (Panel 2-a, hypercoagulable screen.)	Identifies that coagulation has been chronic or ongoing.
protein C	•	•	Endogenous anticoagulants, similar interpretation for all. Low causes thrombosis. High = upregulation in response to ongoing thrombosis, markers of hypercoagulable state.	All four are both hypercoag markers (high) or cause (low). Not always synchronous, so get all for better sensitivity as a general screen, or be selective for items previously altered. Reflex high values should improve when healthy.
protein S	•	•		
antithrombin III	•	•		
plasminogen	•	•	Rises in thrombotic states, marker of ongoing thrombosis.	

			Plasma species. (Panel 3-a, thrombophilic screen.)	Order only those items altered during the morbid state.
factor VIII		•	Potent primary instigator of thrombosis. High causes clot.	As with C-S-AT3, these items can have a fixed or genetic aberrancy making them a root cause primary hypercoag species. More common though are dynamical changes up and down indicating disease subsidence or recurrence.
von Willebrand factor (vWF)		•	Potent thrombogen by f.VIII promotion et al. High = clot.	
tiss. plasm'gn activator (tPA)	•		Low activity equiv. to low plasminogen, propagates clot.	
plasminogen act-inh (PAI-1)		•	High implies low tPA activity impl. low plasmin impl. clot.	
			Immune species. (Panel 3-b, autoimmune screen.)	Order only those items altered during the morbid state.
ANA, w/reflex		•	ANA's mark cvd-ctd's, can wax & wane with disease state.	Order ANA, w/reflex, or single spp. such as rheum factor.
esr, crp, complement		•	Misc markers, acute and chronic inflammation.	Same as managing cvd-ctd's, use to track disease or rx.
antiphospholipid antibodies		•	Basis of hypercoag APLA synd., often assoc. with immune dx.	Some labs use APL in lieu of ordering indiv. ACA-LAC-etc.
anti cardiolipin antibodies		•	ACA: APLAS vector, thrombosis risk high when present.	Order ACA (all - IgG,A,M), or else more specific B2GP.
lupus anticoagulant		•	LAC: the other main APLA, high thrombosis risk.	Order dRVVT or LAC, or the more specific aPT or aPS ab's.
anti neutro. cyto. ab (ANCA)		•	High = marker and also cause of thrombosis, similar to APLA.	Order ANCA's or the specific AP3 (c-anca) or MPO (p-anca).
			Metabolic species. (Panel 3-c, others screen.)	Order only those items altered during the morbid state.
heparin-PF4 Ab (HIPA)		•	Positive antibodies imply thrombic HITT (but not confirm).	Some are thrombic species, others reflect an underlying thrombosis prone disease. All of these tend to vary with status of the disease. Resurgent high values can indicate recurrent hypercoagulable state & thrombosis risk, as well as reflect flareup or activity of underlying disease.
homocysteine		•	High values risk atherosclerotic vascular dx & thrombosis.	
SPEP, etc.		•	Paraproteins imply thrombogenicity from underlying disease.	
CEA, etc.		•	Presence or high suggests occult tumor & Trousseau synd.	
cryoglobulin, cryofibrinogen		•	High risk thrombogenic (viscosity, precipitates, vasculitis).	

Panels 1, 2, & **3** group the tests by physiological and pathological considerations. If workup and diagnosis are falling into one of these categories, then all of the tests in the relevant subpanels can be instructive. **Panel 4** groups are based on a pragmatic approach to workup when there is suspicion of hypercoagulability and a thrombotic state but no clear insight yet as to cause or disease category.

Panel 1-a & 2-a. Order these two for a rapid screen to ascertain or confirm a state of occult or micro thrombosis or hypercoagulability. This is a minimum set of tests which are available in nearly all hospital labs with short reporting times. Use this when there is some immediacy to assess a problem or else as a bare minimum screen to verify or exclude those disorders. If results are positive, then further workup can be ordered or care planned. If results are negative and clinical suspicion is low, then no need of further workup or consideration.

Panel 3. Order tests from the relevant subpanels when initial workup or clinical suspicions are pointing toward specific categories of illness and hypercoagulability. For most patients or situations, first tier tests should suffice to get meaningful diagnostic data. Second tier tests tend to be more expensive and harder to obtain without adding much more to diagnostic sensitivity, specificity, and inclusivity. However, order them when first tier tests are inconclusive, or as required for a more certain or confirmed diagnosis, or for special circumstances or clinical suspicions, or for learning, teaching, and research purposes.

Panel 4-a. Order this when clinical suspicion of hypercoagulability is high and timely results are needed. This set of tests is available in nearly all hospital labs, with short turnaround times, results typically all reported within 24-48 hours. If a patient has a hypercoagulable or microthrombotic disorder, this will likely confirm the diagnosis, even if it does not necessarily identify root causes. The results of this panel will usually suffice to start initial treatment and planning of short term care, such as start of anticoagulants or steroids.

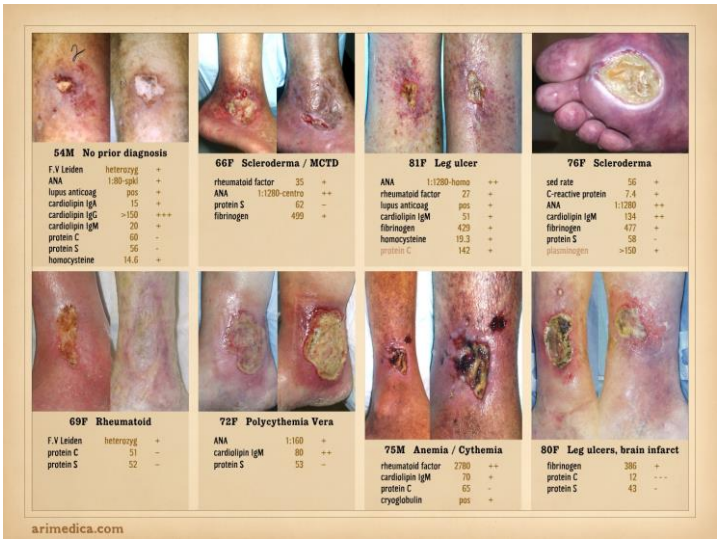
Panel 4-b. Order this when clinical suspicion remains high but is not confirmed on first tier testing, or more commonly when a hypercoagulable disorder has been confirmed but more precise information is needed to assess long term risks and treatment. This set of tests includes many that are "send outs" that must go to commercial reference labs, and reporting times can be as long as 3-4 weeks. Thus, they cannot assist you for short term assessment and treatment, but they can identify primary disorders that will influence long term patient management.

Gene tests. Factor V Leiden and prothrombin 20210G are sufficiently prevalent and commonly encountered on workup that they can be included in first round testing (Panel **4**-a) recognizing that they will not be reported as quickly as the others. MTHFR gene can also be included, but homocysteine is a better as a screen, just as APC resistance screens for f.V Leiden. The gene tests only need to be ordered once in a patient's lifetime.

Hands on tests. Bleeding time, tested directly on the patient, and whole blood clotting time in a test tube are so easily done that they should be. These are done "hands on" by the practitioner. Bleeding time can be observed with every debridement or operation, so make a habit of timing it during these events. Histology is not always safe to do in some pathergy prone ischemic conditions, but when eligible or after a debridement, submit materials to the lab for microscopic examination. (Concerning activated clotting tests such as aPTT and PT-inr, these are validated and relevant for managing hypocoagulable disorders, not so much for hypercoagulability. They typically are not included in hypercoagulable workup or lab panels, but if you do one of these tests and it is unusually rapid, it can then be a valid marker for that particular patient.)

Panel 4-c. These items are not part of a general hypercoagulable workup. They are markers of very specific diseases that cause excessive clotting, diseases usually diagnosed by distinctive or pathognomonic clinical features, and the tests are meant to be used for diagnosis or followup of those specific disorders. They need not be included in general hypercoagulability screens or followup.

Panel 4-d. Items on this panel are for long term followup and maintenance, intended to confirm that prior hypercoagulable states remain quiet, or to evaluate suspected flareups of the coagulopathic state or the underlying cause. The direct and reflex markers are simply repeats of **Panels 1-a** and **2-a**, the most basic screens of final common markers of thrombosis and thrombosis risk. The difference between first time or acute workup versus longitudinal followup is that when the maintenance screens are done, the diagnosis is already established and you are simply looking for evidence of flareup or quietude. Aside from the full set of direct and reflex markers, order only those other items which are known to be relevant to the patient's specific diagnosis or which were previously abnormal during the acute morbid phase.



13
Case Studies in Laboratory Interpretation

These cases are further exercises in how to asses abnormal lab tests related to hypercoagulable disorders. Remember that many hypercoagulable patients have autoimmune cvd-ctd's, and vice versa, that autoimmune disorders are part of the syndromic hypercoagulable pentad, and that chronic pathological wounds might have thrombo-infarctive or inflammatory-lytic features but often both. This means that, based on clinical features, it is sometimes pertinent to order just one set or the other of screening panels, hypercoagulable or autoimmune, but for many wounds and patients, both should be ordered, and both will have positive or abnormal values.

Top 1 (left). 54 yo man, leg ulcers, no prior diagnosis. Thrombo-infarctive pattern of ulceration, with periwound cyanotic stasis, progressive ulceration, and free of inflammatory erythema and edema. *Lab shows: Factor V Leiden = heterozygous, ANA = 1:80-speckled high, lupus anticoagulant = positive, cardiolipin IgA = 15 high, cardiolipin IgG = >150 out-of-range high, cardiolipin IgM = 20 high, protein C = 60 low, protein S = 56 low, homocysteine = 14.6 high.* The gene mutation is a system root, so all other changes must derive from that. Low C & S promote thrombophilic thrombosis. Homocysteine is a prothrombotic metabolic stress. Not only are the anticardiolipins and lupus anticoagulants high, potent causes of hypercoagulability, but in conjunction with positive ANA, these are indications that the hypercoagulable disorder has bred an autoimmune state.

Top 2. 66 yo woman, active scleroderma and mixed connective tissue disorder. Ulcer features are mixed but mostly inflammatory-lytic. *Lab shows: rheumatoid factor = 35 high, ANA = 1:1280-centromere high, protein S = 62 low, fibrinogen = 499 high.* High serologies confirm the autoimmune state while hinting that her disease is partly lupus or mixed ctd which is consistent with general history and exam. Low S is thrombogenic, and high fibrinogen is common in active hypercoagulable states. Wound improved with anticoagulants, steroids, and surgery (biomatrices).

Top 3. 81 yo woman, leg ulcer without prior history. Lesions show vascular stasis and mostly thrombo-infarctive pattern of ulceration but with some gross inflammation. *Lab shows: ANA = 1:1280-homogeneous high, rheumatoid factor = 27 high, lupus anticoag = positive, cardiolipin IgM = 51 high, fibrinogen = 429 high, homocysteine = 19.3 high, protein C = 142 high.* There are no primary thrombophilic markers. Autoimmune serologies are high, so it is not surprising to see also presence of procoagulant antiphospholipid antibodies. Fibrinogen is high "as always", but protein C being high indicates a reflex upregulation to serve its purpose as an endogenous anticoagulant in response to the hypercoagulable state.

Top 4. 76 yo woman, scleroderma, and history of pulmonary thromboembolism. *Lab shows: sed rate = 56 high, C-reactive protein = 7.4 high, ANA = 1:1280 high, cardiolipin IgM = 134 high, fibrinogen = 477 high, protein S = 58 low, plasminogen = >150 out-of-range high.* General markers of inflammation sed rate & crp are high, not attributable to this small grossly non-inflamed foot wound. Serologies confirm her connective tissue disorder, and high cardiolipins are a hypercoagulable manifestation of this autoimmunity. Protein S is low rather than reflex high, so it is contributing rather than responding to the hypercoagulable state. As always, fibrinogen is high, and the hyper-thrombotic state make micro-thrombi is reflected in the upregulated plasminogen value.

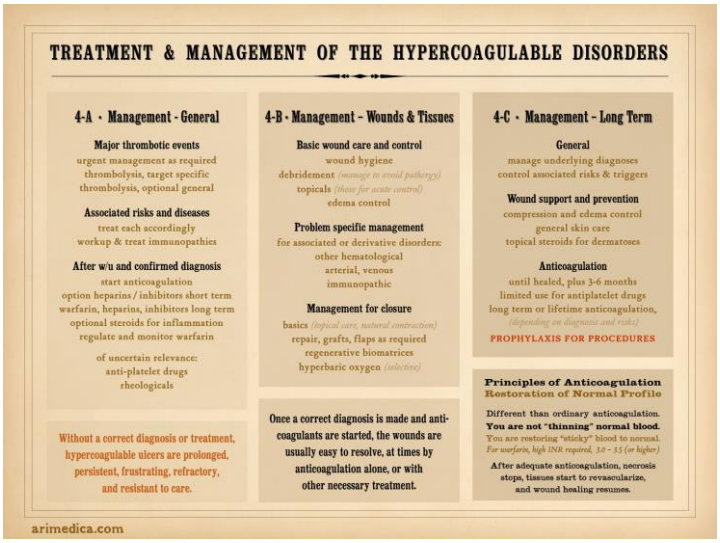
Bottom 1. 69 yo woman, active rheumatoid, ankle ulcer immediately following hip surgery. *Lab shows: Factor V Leiden = heterozygous, protein C = 51 low, protein S = 52 low.* Pattern is pure inflammatory-lytic, as expected since this was induced by remote injury, an inflammatory "crossover" or remote immune trigger. Proteins C & S are low, which along with the altered gene are potent markers of hypercoagulability. She healed with anticoagulants and biomatrices.

Bottom 2. 72 yo woman, polycythemia rubra vera with an ankle ulcer. *Lab shows: ANA = 1:160 high, cardiolipin IgM = 80 high, protein S = 53 low.* Immune serologies are high, and the high anticardiolipin confirms a hypercoagulable state, along with added pro-thrombotic stress from a low protein C. This is consistent with the mixed appearance of the wound. Both views show inflammation with edema and erythema. On the right, the condition has flared up, with more inflammation but also signs of vascular stasis and infarction. Around the perimeter can be seen zones showing both lytic and infarctive ulceration at the skin edges, indicative of both micro-thrombotic as well as immune-inflammatory modes of injury.

Bottom 3. 75 yo man, currently anemic but with a history of a hypercythemia not further specified. *Lab shows: rheumatoid factor = 2780 high, cardiolipin IgM = 70 high, protein C = 65 low, cryoglobulin = positive.* High anticardiolipins, low protein C, and presence of cryoglobulins indicate that he is hypercoagulable and micro-occlusive. Antiphospholipids implies some degree of autoimmunity, confirmed by very high rheumatoid factor. His history of some sort of hypercythemia or other formed element hematopathology implies a micro-occlusive disorder, even if not a hypercoagulable one. Odds are that the chronic micro-occlusive disorder was the breeder disease for the secondary auto-immunopathy.

Bottom 4. 80 yo woman, leg ulcers, cva brain infarct. *Lab shows: fibrinogen = 386 high, protein C = 12, low, protein S = 43, low.* Wound has mixed inflammatory and thrombotic features, lysis and infarction. Wound edges are lytic, whereas infarcted areas are within central areas and superficial layer of previous wound module or granulation tissue. This implies that autoimmune disease and lysis are primary, with the hypercoagulable state compounding the problem and infarcting tissues that were trying to heal. High fibrinogen is consistent with the hypercoagulable state, so too proteins C & S. Protein C being exceptionally low implies it is the primary abnormality in the current hypercoagulable state.

Notice how the lab tests have certain consistent patterns. There are markers of the thrombotic state, markers of reflex response to the intravascular thrombosis, markers of an unbalanced coagulation system wherein arises the hypersensitivity to trigger clotting, and markers of species that are causing the triggering or unbalancing the system. The frequent combination of coagulopathy or other micro-occlusion with autoimmunity is profound. The auto-immunity is often, perhaps mostly, a secondary consequence of the primary thrombotic or occlusive disorder. Often, on the lab profile, the thrombophilic plasma protein problems can be discriminated from the immune or metabolic or other micro-occlusive disorders, or the pathogenic order inferred. Other times, the lab findings seem unaligned or misaligned in relationship to clinical history and physical findings. If only a few tests were ordered as a screen, a second round of more complete testing might resolve the features and diagnosis. Either way, finding several relevant positive tests is usually sufficient, in conjunction with clinical profile, to initiate anticoagulant therapy or anti-inflammatory therapy or frequently both.



14
Treatment & Management of the Hypercoagulable Disorders

Treatment of hypercoagulable disorders and wounds have several modes. These include management of major large vessel events, anticoagulation, treatment of associated immune or other disorders, and then management and closure of the wounds.

This panel summarizes the treatment approach to hypercoagulable disorders, patients, and wounds. Management must address the wound, the whole patient, the coagulopathic state, and any underlying or associated disease. Be cognizant of how the patient presented. Large vessel thromboses with major organ or limb infarcts need urgent intervention. It is too easy to overlook the possibility that a hypercoagulopathy caused the infarct and then forget to work it up, especially since the patient might well be on anticoagulants afterward. Under such circumstances, anticoagulants can mask the problem, postpone further troubles until patient is out of the hospital and possibly off the drugs again, or risk infrequent but serious problems such as warfarin necrosis. If however the patient presents with a slow surreptitious micro-thrombotic problem, the diagnosis might be overlooked and proper treatment denied. Alternately, if the coagulopathic diagnosis is made, do not err in just treating that and ignore the need for proper diagnosis-independent wound care. Do not fail to recognize the collateral diagnoses and treat them, such as the autoimmune inflammatory states or disorders. For patients who have them along with the hypercoagulable problems, treatment will depend as much on giving steroids concurrent with the anticoagulants. Also, giving heparin will, with few exceptions, reliably and immediately correct a state of hyperthrombotic imbalance and arrest clotting. This does not mean though that the inherent tendency to clot has subsided, so the true problem must be subsided as well, which means proper wound care, steroids or anti-immune therapies, or whatever else is relevant to each patient's specific condition.

4-A • Management – General. Treat the ***major thrombotic events.*** Treat the acute life and limb threatening presenting events as dictated by circumstances. Modern technologies to treat these problems are extraordinarily good, using surgery, thrombectomy or thrombolysis, and other catheter directed interventions. (The biggest challenges these days is responding to the problem and getting the patient to the point of service as rapidly as possible.) Thrombolysis if opted can be target specific or general. Anticoagulation or anti-platelet therapies or both are likely to be started. If there is any discrepancy between actual and expected angiographic or surgical findings or response to treatment, review the possibility of a hypercoagulable state and work the patient up as soon as practical. For example, if a heart catheterization for acute coronary thrombosis reveals clot but no atheromas, especially in a young person or with a similar family history, then a hypercoagulable disorder is virtually certain. Being on anticoagulants will alter some of the coagulation tests that you want to order, but not all, and laboratory diagnosis might still be made. ***Associated risks and diseases.*** Treat each accordingly. If the hypercoagulable state was a paraneoplastic complication, the cancer needs treatment. If the patient has paraproteinemias or hemoglobinopathies, patient might need hemodilution with fluids or even plasma- or erythropheresis. Such examples are infrequent, so all the more reason to be aware of them to recognize and manage them when seen. Any concomitant vasculopathy or altered flow state or other micro-occlusive disorder needs correction. If the patient presents with a venous stasis ulcer, as benign as that is with respect to general health, it needs its own proper treatment with compression and wound care. However, the "big dog" of comorbid illnesses are the autoimmune collagen-vascular connective tissue disorders. Not only do they need treatment in their own right, but due to the strong interdependence of the coagulation and inflammation domains, treatment of the inflammation and autoimmunity can be considered as essential to the treatment of the coagulopathy itself and its immediate complications, be it a vasculitis or ulcer or thrombosis.

After workup and confirmed diagnosis, start anticoagulation. Choices will be dictated by circumstances, and particular choices are more likely to be based on collateral patient management issues rather than anything inherent about the drugs themselves, such as inpatient versus outpatient, patient is permitted oral intake or not, or allergy or adverse reaction to a particular agent. For the highest stakes problems where the most rapid or potent control is needed, heparins are always the preferred choice, although recent experience with alternative intravenous agents such as argatroban seem to be equally effective. Up until circa 2010-2015, this discussion had solely two options to talk about, heparins (including their low molecular weight derivatives more suitable for subcutaneous administration) and the dicoumarol derivatives (of which only warfarin has been relevant since circa 1980). There is now the class of direct thrombin inhibitors which not only provide useful alternatives when heparin and warfarin cannot be used, but are finding their own righteous place in the scheme of long and short term anti-thrombotic management. When warfarin is used for outpatient or long term management, it must be monitored and regulated, although with the caveat that it might prove difficult to regulate in the face of the hypercoagulable disorders, at times necessitating switchover to alternative agents. To reiterate, steroids are essential concurrent drugs for patients with active autoimmune and inflammatory states.

There are other agents to help manage micro-occlusive disorders which might be quite relevant for specific diagnoses but which are ***of uncertain relevance*** for the pure hypercoagulable and thrombophilic disorders. ***Anti-platelet*** drugs, such as aspirin and clopidogrel, have proven their value for treating various macro- and micro-vasculopathies where platelet activation and aggregation on thrombogenic surfaces are equally or more likely to be the clot forming culprit rather than plasma protein activation. However, for the typical primary or pure hypercoagulable state where the problem is altered plasma protein balance or function, anti-platelet drugs are generally not useful or at least not overt or dramatic in their effects. In a patient with a hypercoagulable disorder who coincidentally has an angiopathy, then anti-platelet drugs plus anticoagulants might indeed be considered. ***Rheological agents*** have a more uncertain or nebulous role to avoid thrombosis, not so much because they do or do not work or that the science and hypothetical uses are valid or invalid, but because they are used and studied so infrequently that it is hard to infer a clear set of indications or how well they work. These are meant to improve the flow characteristics of blood in small or altered vessels, by lowering viscosity or diminishing turbulence. One thing in that regard that is dependable is simply lowering the hematocrit. The circumstances that bring wound and thrombotic patients to attention are more commonly associated with chronic illness where anemia or erythropenia are more likely. However, other patients also get hypercoagulable problems, and if by happenstance they have polycythemia or erythrocythemia or hemoconcentration, then that needs a correction. If the thrombotic event occurred in conjunction with hemoconcentration (and associated low blood pressures and low flow velocities), such as after exposure dehydration or diarrhea, then rehydration is crucial and will correct all of the ills. If a polycythemia is the problem in the face of euvolemia, then phlebotomy and removal of blood with fluid replacement down to a lower hematocrit is required. If altered flows due to high viscosity result from hyper- or paraproteinemias, then plasmapheresis or plasma exchange will help. For pharmacological reduction in blood viscosity and improved hemorheology, mannitol is the agent to be used for urgent, inpatient, intravenous administration, and pentoxifylline is the drug to be used for oral and long term use.

4-B • Management – Wounds & Tissues. There are certain common principles of ***basic wound care and control*** that apply to all wounds and ulcers regardless of etiology. These begin with good wound hygiene, debridement, topicals, and control of edema and inflammation. These principles are so foundational in wound care that details will not be further presented here. Note that "topicals" refers to basic passive items to control or maintain a wound, not pharmaco- or bioactive or biological products meant to be used at a later non-acute time to stimulate or accelerate wound healing. An explicit word is required though about debridement. While debridement is normative for wound management, it is also an injury, and in pathergy prone subjects, otherwise proper safe debridement can trigger more infarction. In such patients, whether due to hypercoagulability or vascular disease or autoimmune and inflammatory states, correcting the problem with anticoagulants or steroids before doing biopsies or debridement is always a prudent first step, after which the procedures can be done safely.

Once basic wound care has been started and started, it is also essential to treat the underlying or causative disorder[s]. ***Problem specific management*** will of course vary with what the problem is. However, many wound diagnoses can be excluded from this discussion. A person with a pressure ulcer or a burn injury could coincidentally have a coagulopathic or hyperthrombotic disorder, in which case both need to be managed, but the association is purely coincidental. When a wound is associated with a hypercoagulable state, the underlying or collateral disorders that require attention, either because there is some cause-and-effect relationship or because their coincidental occurrence amplifies the thrombotic risk include: other hematological disorders, any arterial, venous, or other vascular disease, and immunopathic and other active inflammatory disorders. The important interactions of thrombotic and immune disorders has already been amply emphasized, but there are also non-obvious aspects to this relationship. For example, patients with rheumatoid and lupus ulcers of the lower extremity are at risk for reulceration due to crossover inflammation. This is where lymphoid tertiary organs (lymphocytes and plasmacytes) are resident in a chronic wound, typically as perivascular aggregates. This is a hallmark feature of immunopathic non-healing wounds, and these lymphoid bodies will persist even after the hard-to-heal wound has healed. When some other remote acute inflammatory event occurs, endocrine effects of circulating lymphokines and other inflammatory chemistry will "wake up" these aggregates which in turn martial neutrophils which are responsible for the inflammatory-lytic reulceration which then occurs. This tends to have a seasonal incidence, occurring during winter cold and flu season or during springtime allergy season. Giving such patients seasonal short courses of steroids or other anti-immune or anti-inflammatory drugs can be important, keeping in mind that all of these risks and responses are aggravated or amplified in patients with hypercoagulable disorders.

Management for closure, since for wounds, that is the ultimate goal. Since this presentation is not about wounds per se, the discussion here is brief. Principles of wound closure fall into certain standard paradigms. They can close spontaneously, in which case the goal of care is to maintain hygienic and non-morbid conditions so that nature can do its work, i.e. basic and topical care in support of natural contraction and epithelialization. When the indications are there for surgical closure, via the three basic paradigms of simple repair, flaps, and grafts, then the main imperative is to keep coagulopathic and immunopathic and other pathergy provoking conditions under good control, as strict as possible. ***Regenerative biomatrices*** are the newest paradigm of operative wound closure, extant since 1996, and becoming ever more relevant. These products, acellular scaffolds from biological sources, allow host cells to repopulate them and form new autogenous fascias according to tissue dynamics that are similar to embryonic histogenesis rather than post-inflammatory wound healing and scar. Since these products are not alive when applied, but they afford the benefits of biological coverage, they tolerate imperfect conditions, allow biological recovery of the host wound, and then regenerate into host tissue. They are highly resistant to or suppressive of wound pathergy, and as such, they have become a quintessential element of successful surgical wound closure when dealing with CAP wounds ("chronic and pathological") due to pathergy prone wounds arising from the lytic conditions (inflammation, auto-immunity) and the ischemic thrombo-infarctive conditions (macrovascular disease, micro-occlusive disorders, hypercoagulopathies). As discussed on a pending panel, they have become a highly dependable and indispensable modality of care of hypercoagulable ulcers and infarcts. ***Hyperbaric oxygen*** is also relevant to some of these patients. This modality is not a wound panacea, but despite its well publicized overuse and abuse for non-indicated conditions, it has an important purpose for certain wounds, primarily those that are ischemic. As an adjunct to surgery and biomatrices, it can make a difference in select patients to ensure revascularization and recovery of the affected tissues and allow the wounds to heal, in conjunction with basic wound care, good clean surgery, and anticoagulation.

4-C • Management – Long Term. Patients with hypercoagulable disorders will often present for the first time, or when the diagnosis is first made, because of some urgent or at least morbid condition that makes them seek help. The short term focus is thus on the presenting issues. However, these patients have built n or long term risks, so even after the acute events are recovered, the patients need long term management to suppress the problem and avoid further morbid complications. ***General management*** must be done, meaning that if there is a recognized or diagnosed primary or causative disorder or other associated disorders, then they must have ongoing management to keep them quiet, under control, and with

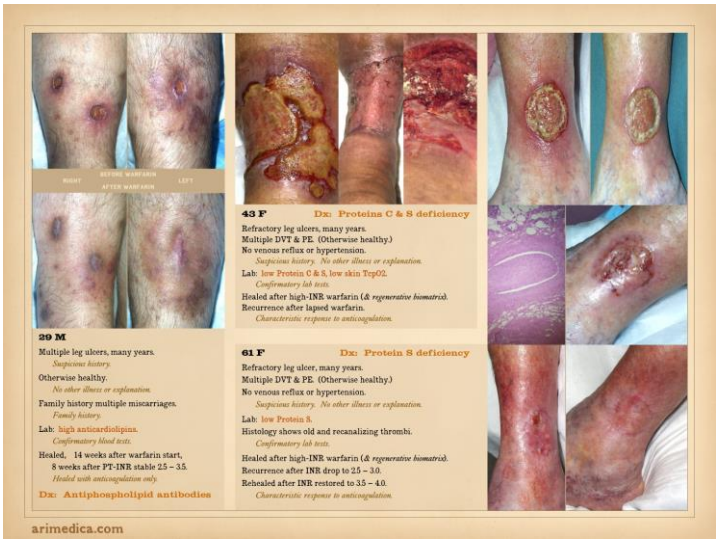
minimized likelihood of misbehaving and causing a new round of complications. For hypercoagulopathies, anticoagulant administration will likely (but not always) be a part of this long term management. Any other comorbidity or risk factors or trigger conditions that are identified should also be managed or suppressed, not just for the avoidance of thrombosis, but for the general health and habilitation of the patient.

If the presenting or one of the active or prior problems is a wound, then the patient needs generic wound maintenance or preventive care. One of the common scenarios where coagulopathic wounds are chronic or chronically managed are those associated with chronic venous disease. (Remember that a lot of chronic venous disease is not so simple, that it results from hypercoagulable induced venous thrombosis, and then once the ulcers are established, the coagulopathy predisposes to pathergy and progressive inflammation, and it impairs healing.) ***Wound support and prevention*** for healed venous ulcers is as simple as faithful use of compression wraps or stockings for edema control. Good hygiene, general skin care, proper topical care of residual wounds, and ad hoc topical steroids for any residual inflammatory dermatosis are the simple basics of effective long term maintenance care.

Anticoagulation is the main modality to treat hypercoagulable disorders. It is the first, necessary, and quintessential element of care for these patients and problems. The question arises how long the anticoagulation should continue? There are several options which must be gauged with respect to the nature or cause of the hypercoagulable state and the severity of the complication or presenting problem. The answers must also be measured against the understanding that patients with hypercoagulable disorders or risks are not always in a hypercoagulable state, and that there are times when anticoagulation is not strictly necessary. On the other hand, if the patient has become blind from a retinal artery thrombosis, or has multiple lacunar infarcts in the brain, or has had non-atheromatous coronary occlusion, or survived Budd-Chiari hepatic thrombosis, then the risks are too high to "go bare" without treatment. Whenever the risk of the disease outweighs the risks or nuisance factor of managing the anticoagulation, then treatment is needed. The answers will mostly fall into these options: ***(1) Short term*** use during the acute phase of injury and ulceration. If the patient has risks or caveats to using anticoagulants, then using them as short as practical can be considered. It is hard to imagine scenario in which this would apply, so it can largely be ignored. ***(2) Life of the ulcer until resolved.*** This might seem logical in some ways, but it ignores the biology of the nominally "healed" wound. If the patient tolerated their anticoagulation this far into their care, there is little reason to stop it at this point. ***(3) Life of the ulcer and then some until the wounds and scars are mature.*** Complete epithelialization is the nominal endpoint of wound healing for practical every day purposes, but it is far from the "end of the road" of the biological processes in that zone. Young scars have considerable biological activity including significant alterations in the local vasculature as the excessive vascular density of the healing wound gets remodeled away. The author's practice is to maintain anticoagulation after the wounds are epithelialized. For high risk patients, this could be lifelong, but for low risk patients in-and-out of a thrombotic attractor, therapy is maintained until scars are mature, back to normal color and mechanical compliance, the usual indication that biological activity has subsided to some stable baseline. This is typically 3-12 months depending on many parameters of patient demographics and the disease being managed. ***(4) Long term or lifelong.*** As implied above, conditions or patients who have already experienced or are at high risk for life-or-limb disabling events should remain on anticoagulation indeterminately long or forever. ***(5) No maintenance therapy, but ad hoc use.*** For patients at relatively low risk or who remain non-hypercoagulable at most times, then it is fair to use anticoagulants only incidentally before or during risky events such as surgery or trauma. Prophylactic use of anticoagulants for elective procedures, or as soon as feasible after trauma or emergency surgery, should be considered the norm. Remember that these disorders are highly pathergy prone, and anticoagulants are the specific prophylaxis against this. If the patient has no prior history, then the problem cannot be predicted, but once it has happened, workup should identify the problem and permit treatment. For patients with a known hypercoagulable disorder, especially with a history of a pathergy event or wound or surgery complications, prophylactic anticoagulation should be considered mandatory.

Like everything else in medicine, ***wrong diagnosis*** means wrong treatment means no or bad result. Without a correct diagnosis or treatment, hypercoagulable ulcers are prolonged, persistent, frustrating, refractory, and resistant to care. Once a ***correct diagnosis*** is made and anticoagulants are started, the wounds are usually easy to resolve, at times by anticoagulation alone (plus "basic" wound care), or anticoagulation with other specific treatments relevant to specific circumstances (e.g. steroids for the concurrent autoimmune disorder or hyperbaric oxygen or surgery).

There is an important caveat about anticoagulants in these patients, a key to effective use that distinguishes hypercoagulable patients from normal people. The goal of treatment is not so much to anticoagulate these patients, but rather to ***restore a normal clotting profile***. While this might sound unnecessarily semantical, there is a crucial meaning here. Consider a prototypical use of heparin to prevent femoral vein thrombosis after hip surgery or to prevent mural thrombosis from atrial fibrillation. These patients have normal blood and normal coagulation. They are at risk for thrombosis due to local alterations of hemodynamics or inflammation and injury. Normal blood is tuned not to clot inside normal vessels, but in these two examples, the blood vessels are not normal. Their slight abnormality creates a trigger for the normal blood. With proper anticoagulation, (1) the blood will be just "thin" enough to make it less sensitive to those weak triggers so that it acts normally while passing those zones, but (2) the blood is not "broken", and it will clot properly when facing an appropriate challenge such as a traumatic hole in a blood vessel. If using warfarin, proper adjustments are achieved when the prothrombin time INR is about 2.0 – 2.5. In contrast, hypercoagulable blood is differently tuned. It is likely to self-trigger even when flowing smoothly along entirely normal vascular endothelium. The goal for these patients is to restore "sticky" blood to a normal clotting profile. At the proper level, the treated blood will behave like normal blood, such that it will not clot within the blood vessels but can still clot properly when properly challenged by injury. Anticoagulant use in these patient is thus ***different than ordinary anticoagulation. You are not "thinning" normal blood. You are restoring "sticky" blood to normal.*** For warfarin, this typically happens when the INR value is about 3.0 - 3.5, sometimes higher. After adequate anticoagulation, necrosis stops, tissues start to revascularize, and wound healing resumes.



Case Studies, Care and Management

The integrated or comprehensive approach to the hypercoagulable wound can be best appreciated by studying a variety of cases. The cases on this panel show a diverse set of hypercoagulable patients, lesions, and coagulopathic diagnoses.

This panel has case studies. The focus here is not so much about recognition and diagnosis, as it was on preceding panels, rather the focus here is about treatment approaches and results of care. In the description of each patient, an item of history, exam, or lab is stated, *(and then in parentheses that information is categorized with respect to making the diagnosis or details of treatment).*

Left.	**29 year old man.**
History:	Multiple leg ulcers, many years *(suspicious history).*
	Otherwise healthy *(no other illness or explanation).*
Family hx:	Multiple miscarriages *(positive family history).*
Lab:	Anticardiolipins high *(confirmatory blood tests).*
Diagnosis:	Antiphospholipid antibodies.
Treatment:	Warfarin anticoagulation *(and basic topical wound care).*
Outcome:	Healed, 14 weeks after warfarin start, 8 weeks after PT-INR stable at 2.5 – 3.5 *(healed with anticoagulation only).*

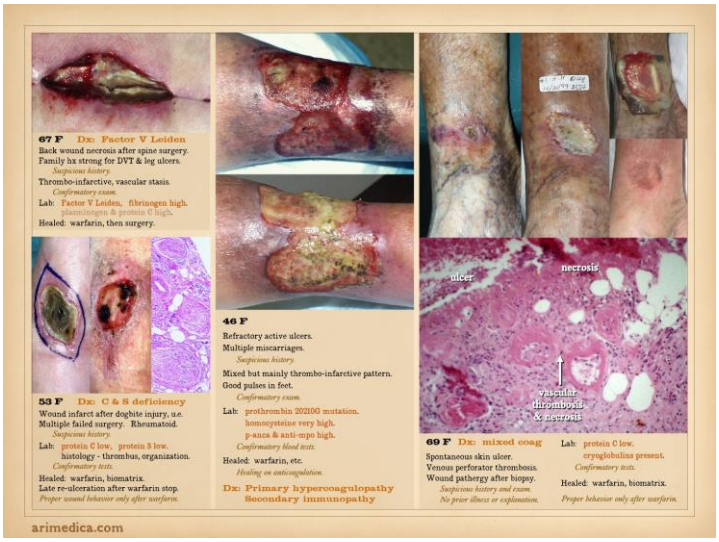
This case illustrates: a suspicious history given his young age; a positive profile for the pentad hypercoagulable syndrome; a lab test confirming a hypercoagulable species (antiphospholipid antibody immune procoagulant). If we discount the etiology, for example if these were minor superficial trauma wounds in a healthy patient, they would heal by natural contraction supported by basic hygienic wound care. That is all this patient had, basic wound care, plus warfarin anticoagulation to counteract the hypercoagulable state. That was all that was required for these wounds to heal.

Center.	**43 year old woman.**
History:	Refractory leg ulcers, many years, and multiple DVT & PE *(suspicious history).*
	Multiple DVT but no venous reflux or hypertension *(no other illness or explanation).*
Lab:	Proteins C & S low, skin TcpO2 low *(confirmatory tests).*
Diagnosis:	Proteins C & S deficiency.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed after achieving high PT-INR 3.5 – 4.0 *(healed with anticoagulation and biomatrix).*
	Recurrence after lapsed warfarin *(characteristic response to anticoagulation and then lapse in treatment).*

This case illustrates: a suspicious history of refractory wounds plus thrombotic and embolic events; a lab test confirming a hypercoagulable species (direct thrombophilic alteration), and a test confirming periwound skin ischemia. Wounds healed by the dependable combination of anticoagulation plus a regenerative biomatrix. These biomatrices are indispensable for managing these disorders because, not being alive when they are placed, they tolerate imperfect conditions that a skin graft would not survive, but they also induce histogenesis and revascularization thereby correcting the anatomical deficits (as long as the primary disorder is controlled, in this case by warfarin). Wounds relapsed after patient stopped taking warfarin. This confirms ongoing pathological risk and the need for long term anticoagulation.

Right.	**61 year old woman.**
History:	Refractory leg ulcer, many years, and multiple DVT & PE *(suspicious history).*
	Multiple DVT but no venous reflux or hypertension *(no other illness or explanation).*
Lab:	Protein S low *(confirmatory tests).*
Histology:	Old and recanalizing thrombi *(confirmatory micro-anatomy).*
Diagnosis:	Protein S deficiency.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed after achieving high PT-INR 3.5 – 4.0 on high doses of warfarin *(healed with anticoagulation and biomatrix).*
	Recurrence after INR drop to 2.5 – 3.0 *(characteristic difficulties managing warfarin dose).*
	Rehealed after INR restored to 3.5 – 4.0.

This case illustrates: a suspicious history of refractory wounds plus thrombotic and embolic events; a lab test confirming a hypercoagulable species (direct thrombophilic alteration), and histology confirming chronic microthrombi. Wounds healed by dependable combination of anticoagulation plus a regenerative biomatrix. Wounds relapsed despite consistent treatment, which is itself typical of the hypercoagulable states. Wounds healed again by manipulating the warfarin dose, but patient needed high doses (~20 mg daily), which is also characteristic of these disorders.



16
Case Studies, Care and Management

The integrated approach to the hypercoagulable wound is best appreciated by studying cases. Those on this panel show another set of mixed hypercoagulable patients, lesions, and coagulopathic diagnoses.

More case studies. The focus here is about miscellaneous features of hypercoagulable infarcts and ulcers, and their responses to treatment.

Left top.	**67 year old woman.**
History:	Back wound necrosis after spine surgery *(suspicious hx).*
Family hx:	Strong for DVT & leg ulcers *(positive family history).*
Exam:	Thrombo-infarctive, vascular stasis *(confirmatory exam).*
Lab:	Factor V Leiden, fibrinogen high *(confirmatory, direct).*
	Plasminogen & protein C high *(confirmatory, indirect).*
Diagnosis:	Factor V Leiden.
Treatment:	Warfarin anticoagulation *(and surgery).*
Outcome:	Healed, after warfarin then surgery *(allowed safe surgery).*

This case illustrates: unexpected thrombo-infarctive complication of elective surgery absent other problem or personal history; strong family history of thrombosis and ulcers; a lab test confirming a hypercoagulable species (thrombophilic root gene) plus others that are reflex markers of active thrombosis. Wounds healed (not illustrated) and stable long term, by anticoagulation permitting subsequent safe and effective surgery.

Left below.	**53 year old woman.**
History:	Wound infarct after dogbite injury, upper extremity; multiple failed surgery; rheumatoid arthritis *(suspicious history).*
	Multiple DVT but no venous reflux or hypertension *(no other illness or explanation).*
Lab:	Proteins C & S low *(confirmatory tests).*
Histology:	Multiple micro-thrombi and organization *(confirmatory micro-anatomy).*
Diagnosis:	Proteins C & S deficiencies.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed *(with anticoagulation and biomatrix).*
	Late re-ulceration after warfarin stop *(proper wound behavior only with warfarin).*

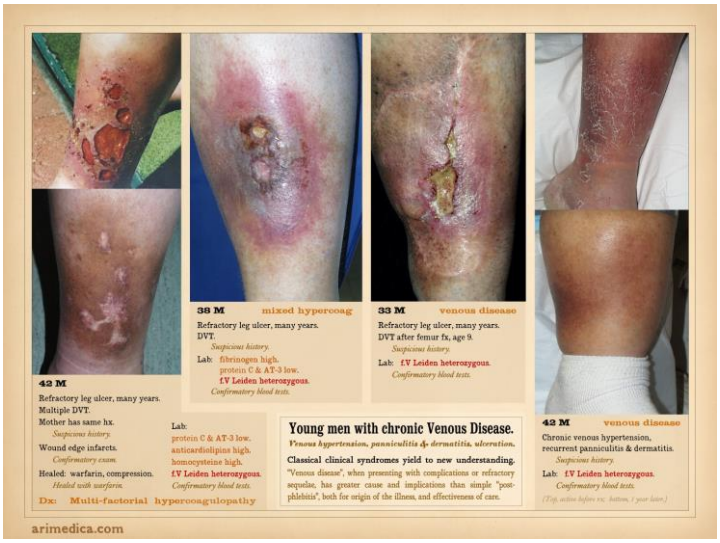
This case illustrates: thrombo-infarctive wound pathergy after trauma in a zone ordinarily not prone to ulceration; autoimmune history positive; blood tests and histology confirmatory (direct thrombophilic alteration). Wounds healed (not illustrated) by anticoagulation and surgery, but wounds unstable, sensitive to warfarin regulation (typical of hypercoagulable states).

Center.	**46 year old woman.**
History:	Refractory active leg ulcers; multiple miscarriages *(suspicious history).*
Exam:	Mixed but mainly thrombo-infarctive pattern *(confirmatory exam).*
	Good pulses in feet *(no other illness or explanation).*
Lab:	Prothrombin 20210G mutation, p-anca & anti-mpo high, homocysteine very high *(confirmatory tests).*
Diagnosis:	Thrombophilic gene disorder (20210G), plus anti-phospholipid antibodies, and mixed profile.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed after warfarin and surgery *(healed with anticoagulation and biomatrix).*

This case illustrates: chronic refractory ulcers with thrombo-infarctive pattern without evidence of macro-vascular disease; a positive profile for the pentad hypercoagulable syndrome; positive lab test (thrombophilic root gene) plus others implying a primary hypercoagulopathy with secondary immunopathy. Wounds healed (not illustrated), by dependable combination of anticoagulation and regenerative biomatrix.

Right.	**69 year old woman.**
History:	Spontaneous skin ulcer; venous perforator thrombosis *(no other illness or explanation).*
	Wound pathergy and ulcer after biopsy. *(suspicious history and exam).*
Exam:	Good pulses in feet; no varicosities or signs of venous hypertension *(no other illness or explanation).*
Lab:	Protein C low, cryoglobulins present *(confirmatory tests).*
Histology:	Wound infarction, vascular necrosis, thrombi *(confirmatory micro-anatomy).*
Diagnosis:	Protein C deficiency, and mixed profile.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed after warfarin and surgery *(healed with anticoagulation and biomatrix).*

This case illustrates: a spontaneous skin ulcer following perforator thrombosis not attributable to ordinary venous reflux; no signs of macro-vascular disease; wound pathergy, necrosis and ulceration after ordinary biopsy; lab test confirming hypercoagulable species (direct thrombophilic alteration, and mixed). Proper wound behavior only after starting warfarin. Wounds healed and stable long term, by the dependable combination of anticoagulation plus a regenerative biomatrix.



17
Case Studies, Rethinking & Re-appreciation of Old Diseases

Chronic venous disease has been recognized and treated for a long time, but our modern appreciation of hypercoagulable disorders means we need to rethink the approach to venous disease, since some of it results from hypercoagulable venous thrombosis.

Case studies on this panel are all similar in having factor V Leiden and clinical venous disease. Notice how each of these relatively young patients has some set of the typical signs of chronic venous stasis, including edema, pigment, dermatitis, panniculitis, ulceration. Venous disease may be a common disorder, but it needs updated appreciation about how hypercoagulable disorders influence its pathogenesis and treatment, especially how hypercoagulability contributes to venous thrombosis then perpetuation of the inflammation and ulcers. Any young person with venous thrombosis, venous hypertension, or chronic venous disease and ulceration should be considered to have a hypercoagulable disorder warranting laboratory workup.

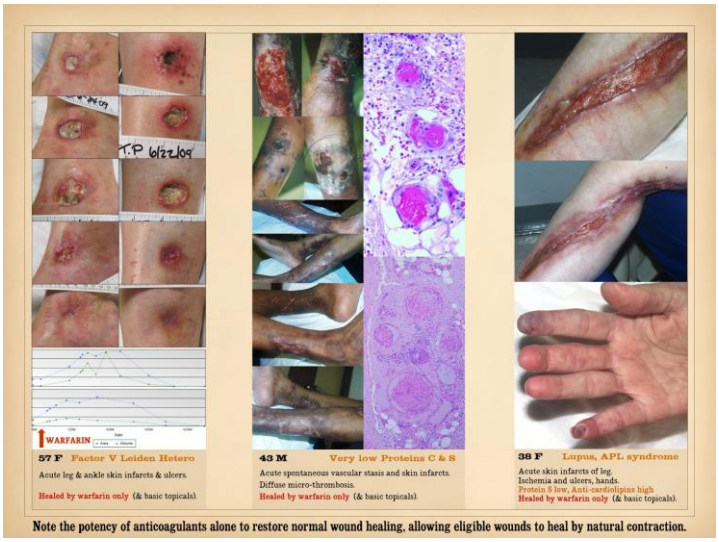
Left.	**42 year old man.**
History:	Refractory leg ulcer, many years, and multiple DVT *(suspicious history).*
Family hx:	Mother has same hx *(positive family history).*
Exam:	Wound edge infarcts, venous stasis features *(confirmatory exam).*
Lab:	Factor V Leiden heterozygous, protein C & antithrombin-3 low, anticardiolipins high, homocysteine high *(confirmatory tests).*
Diagnosis:	Factor V Leiden, mixed hypercoagulopathy.
Treatment:	Warfarin anticoagulation *(and compression).*
Outcome:	Healed with warfarin anticoagulation and usual treatment for venous stasis *(skin and wound care, compression).*

Center left.	**38 year old man.**
History:	Refractory leg ulcer, many years, DVT *(suspicious history).*
Exam:	Wound edge infarcts, localized venous stasis features *(confirmatory exam).*
Lab:	Factor V Leiden heterozygous, protein C & antithrombin-3 low *(confirmatory tests).*
Diagnosis:	Factor V Leiden, mixed hypercoagulopathy.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Followup history not available.

Center right.	**33 year old man.**
History:	Refractory leg ulcer, many years, DVT after femur fracture age 9 *(suspicious history).*
Exam:	Wound edge infarcts, localized venous stasis features *(confirmatory exam).*
Lab:	Factor V Leiden heterozygous *(confirmatory test).*
Diagnosis:	Factor V Leiden.
Treatment:	Warfarin anticoagulation *(and regenerative biomatrix).*
Outcome:	Healed after warfarin and surgery *(healed with anticoagulation and biomatrix).*

Right.	**42 year old man.**
History:	Chronic venous hypertension, recurrent panniculitis & dermatitis *(suspicious history).*
Exam:	Diffuse venous stasis features typical of pre-ulcerated stages *(confirmatory exam).* Top photo, generalized active stasis dermatitis and panniculitis before treatment, focal risk for ulceration Bottom, 1 year later, edema & non-compliant with compression, but resolution of inflammation, no acute events on warfarin.
Lab:	Factor V Leiden heterozygous *(confirmatory test).*
Diagnosis:	Factor V Leiden.
Treatment:	Warfarin anticoagulation *(and compression).*
Outcome:	Inflammation healed, ulcers averted, with warfarin anticoagulation and venous stasis therapy *(skin care, compression).*

These four cases feature men at age 40 who have chronic venous disease. One has history since post-traumatic DVT at age 9. Two others had DVT. One has a family history of the same. All demonstrate localized or generalized features of venous stasis, showing to one degree or another stasis, pigment changes, edema, dermatitis, panniculitis, liposclerosis and fibrosis, and single or multifocal or recurrent ulceration. Unlike many ordinary post-phlebitic ulcers which are otherwise indolent, these show active infarction at the skin edges. One patient was treated in the pre-ulcerative phase, but even he has a zone of dense vascular stasis and cyanosis indicative thrombotic ischemia and risk for ulceration. For any patient with venous stasis disease, there are mandatory principles of care, including high grade compression and edema control for all, and skin care and selective steroids for those with active inflammation. For patients who otherwise have benign hemodynamic reflux with no other problems, that should suffice for healing. ***For this subset with a proven hyperthrombotic state, anticoagulation is required.*** All were treated with warfarin with improvement. In selective cases, wound closure with biomatrices was added to the mix of basic venous stasis therapy plus anticoagulation. Three had long term followup confirming that they are healed. Venous stasis is a classical clinical syndrome, but when "venous disease" presents with complications or refractory sequelae, or an odd history such as young age or family occurrence, then that has broader and more serious implications than simple "post-phlebitis", both for origin of the illness and effectiveness of the care. Always ask the right questions about history.



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

18
Case Studies, Anticoagulants Alone to Restore Wound Healing

Hypercoagulable disorders and their complications must be treated with anticoagulants and other care. This set of cases demonstrates the potency of anticoagulants alone to restore normal wound healing, and allow eligible wounds to heal by natural contraction.

This panel has case studies that emphasize the importance of anticoagulation as the primary modality of treating these disorders and their complications. In each example, the chronic refractory wounds healed after making the correct diagnosis and then using warfarin. In all, the wounds healed using warfarin only (plus basic topical hygienic care), no other specific wound or disease management therapy needed.

Left. 57 year old woman with acute onset multifocal leg and ankle infarcts and ulcers. History and exam warranted hypercoagulable workup which confirmed Factor V Leiden heterozygous. Patient was started on warfarin (and basic topical hygienic wound care), and the wounds healed. The photographs show two ulcers, one already established at the time of presentation, the other showing a zone of thrombotic stasis and infarction which became an open ulcer as the eschar separated leaving the viable tissues behind. The sequence shown takes place over a span of 5 months in which the only active treatment was the warfarin. Wound areas and volumes are graphed below. As is typical, wound size enlarges at the beginning as eschar separates or is debrided and skin elasticity retracts the edges. Time to healing might have been accelerated by use of other supportive modalities suitable for micro-occlusive wounds such as hyperbaric oxygen or surgical closure with biomatrices, or else wound stimulus with biological agents such as autologous platelets or allogeneic amnion. However, none of that was done to keep expenses and logistics simple for the patient, knowing that the wounds would respond to anticoagulation alone.

Center. 43 year old man who also presented with acute onset spontaneous multifocal leg and ankle infarcts and ulcers. History and exam warranted hypercoagulable workup which revealed very low proteins C & S. Histology on biopsies and debrided material showed diffuse micro-thrombosis. Patient healed by warfarin only (and basic topical hygienic wound care).

Right. 38 year old woman with acute skin infarcts of leg, along with ischemic changes of the hands with finger ulcers. As discussed on Panel 6, when Raynaud's phenomenon progresses to infarcts and ulcers, there is already anatomical angiopathy of the lupus-scleroderma type. However, there is also the possibility that there is a concomitant hypercoagulopathy, quite likely due to one of the immune procoagulants, i.e. APL, antiphospholipid antibody syndrome. Patient's workup confirmed diagnosis of lupus, plus protein S low and anti-cardiolipins high. Wounds of leg and hand healed after starting warfarin (and basic topical wound care).

The first patient presented on Panel 15, the 29 year old man, is the same as these three cases in that further infarcts and wounds were suppressed, and existing wounds healed solely by starting warfarin. Aside from basic topical wound care to keep them otherwise healthy, there were no stimulatory therapies or surgery, no biologics or grafts used to implement or expedite wound closure. In the hypercoagulable disorders, infarcts and wounds are a consequence of microthrombosis. If further thrombosis is inhibited, then normal reparative processes will heal the affected site. This means that thrombosed vessels organize or recanalize, and neo-angiogenic revascularization occurs until vascular density and blood supply to the affected tissue is restored to normal. Assuming no other pathologies or problems, then the wounds will contract and epithelialize until closed. Thus, warfarin or any anticoagulant does not have an immediate effect to heal a wound, but it does quickly arrest the root stress in the problem. These cases show the potency of anticoagulants alone to restore normal wound healing, allowing eligible wounds to heal by natural contraction.

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

19
Case Studies, Wound Pathergy and Surgical Complications

Hypercoagulable disorders and their complications are not to be trivialized. Because of their risk of pathergy, with wound infarction and dehiscence, when trauma and surgery interact with them, the results can be extremely morbid, often fatal.

The focus in these case studies is about the extreme morbidity and mortality that are risked when surgery is done on hypercoagulable patients without proper planning or precautions. Recall that wound pathergy, those unexpected and exaggerated adverse response to injury, is risked by a well defined set of conditions. Pathergy is prone in conditions of ischemia and inflammation. This includes macro-vascular disease, micro-occlusive & hypercoagulable disorders, and immune and primary inflammatory disorders. These are the a priori conditions that risk wound complications from trauma and surgery, even something as innocuous as a biopsy or even a needle stick (e.g., Behçet's pathergy test). These are the conditions that mandate not doing indiscriminate

surgery without taking proper precautions before or at the time of surgery, typically using anticoagulants or steroids to control or suppress or obviate the primary risk factors. When trauma and surgery interact with the hypercoagulable disorders, the results can be exasperating, as in the case on Panel 16 ("right" 69 year old woman), but they can also be extremely morbid, sometimes fatal, as illustrated in these following cases.

Left.	**62 year old man.**
Acute:	Diverticular colo-vesical fistula, complicated by anastomotic infarct after ordinary surgery *(wound pathergy).*
	Progressive necrosis of bowel and abdominal wall with repeated surgery *(multiple wound pathergy).*
History:	Finger necrosis after minor trauma. DVT & PE *(suspicious history).*
Lab:	APC resistance high, probably Factor V Leiden *(confirmatory test).*
Histology:	Diffuse micro-thrombi and perivascular infarcts *(confirmatory micro-anatomy).*
Diagnosis:	Hypercoagulopathy (probably factor V Leiden), surgery and trauma induced wound pathergy.
Treatment:	Heparin anticoagulation recommended, but family withdrew care.
Outcome:	Died *(benign primary disorder, but fatal complications of hypercoagulability and wound pathergy).*

Right.	**34 year old man.**
Background:	Systemic lupus erythematosus *(already diagnosed disorder prone to hypercoagulability and pathergy).*
History 1:	Minor hand trauma, then multiple infarcts, ulcers, new wounds from multiple failed grafts and flaps *(multiple wound pathergy).*
History 2:	Wounds after elective hip replacement for lupus arthritis *(pretibial ulcer shown in the photographs, suspicious history).*
Lab:	Anticardiolipins high *(confirmatory test).*
Histology:	Diffuse micro-thrombi *(confirmatory micro-anatomy).*
Diagnosis:	Antiphospholipid antibody syndrome, lupus, surgery and trauma induced wound pathergy.
Treatment:	Warfarin anticoagulation *(and basic topical wound care).*
Outcome 1,2:	Proper wound behavior only after warfarin, all wounds healed *(healed with anticoagulation only).*
History 3:	10 years later: mva, abdominal trauma, abdominal wall infarct with wounds and colon fistula *(repeat pathergy after trauma).*
Outcome 3:	Wounds healed after restart of warfarin, colon fistula managed as a colostomy *(repeat response to anticoagulation).*
History 4:	1 year later: patient again lapsed taking his warfarin, and warfarin was not restarted during this new acute event.
	Ground level fall at home, acute back pain with spine strain-sprain, but without vertebral or neurological back injury.
	Four days later, tardive cord infarct and paraplegia at trauma level, no bleed or compression *(pathergy and infarct in trauma zone).*
Outcome 4:	Permanent paraplegia.

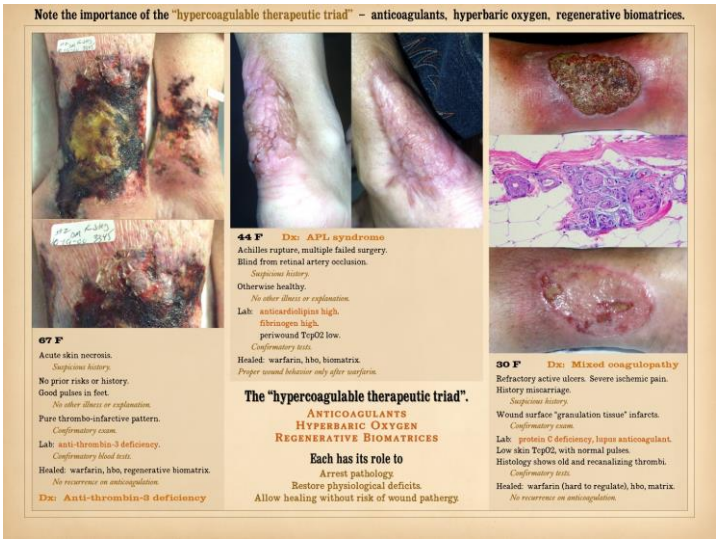
Bottom.	**39 year old man.**
Acute:	Recurrent wounds of feet from minor wheelchair trauma or pressure *(wound pathergy).*
History:	Minor fall, no spine-skeletal injury or cord injury or neurological deficit, then tardive paraplegia in coming days *(suspicious history).*
Exam:	Toes and heels show pure thrombo-infarctive pattern of ischemia and ulceration *(confirmatory exam).*
Lab:	Factor V Leiden *(confirmatory test).*
Histology:	Diffuse thrombosis *(confirmatory micro-anatomy).*
Diagnosis:	Factor V Leiden, trauma induced wound pathergy.
Treatment:	Anticoagulation indicated.
Outcome:	Patient refused therapy, persistent foot ulcers.

Compare these three cases to the two index cases at the beginning of this presentation, a 34 year old man who had progressive surgical wound pathergy eventuating in trans-lumbar amputation following ordinary pressure ulcers, and a 52 year old man who, like the 62 year old man on this panel, had ordinary diverticular disease that resulted in extensive bowel and abdominal wall necrosis following repeated surgery gone bad. For both of these diverticular patients, the surgery was done by extremely experienced capable surgeons, proving that experience and technical skill alone will not prevail over a pernicious hidden disease.

Recall that all ulceration and infarcts can be recognized as either thrombo-infarctive, which implies ischemia, or inflammatory-lytic, implying immunity and inflammation. The only distinction between ordinary ulcers and wound pathergy is that "ordinary ulcers" are the established problems that walk into your office for consultation, and "pathergy" is the set of problems that you witness after deliberately doing something to the patient. For both, the pathophysiology is that there was some focal stress, followed by inflammation or thrombosis or other ischemia, and then ischemic infarction or inflammatory lysis kills the affected tissue. If the tissue was prior normal skin, then you see the later ulcer. If the tissue is the incision you made, then you witness dehiscence. Either way, the propensity to infarct or inflame is heightened in patients who have disorders of coagulation or autoimmunity that alter the trigger point or sensitivity to the exogenous stress conditions.

In these conditions, wound pathergy is a risk. In Nature's eye, there is no distinction between "street" trauma that comes to the office or hospital, and surgical trauma that occurs under controlled circumstances with beneficent intent. In a pathergy prone condition, both will result in inflammation, lysis, infarction, necrosis, dehiscence. If the affected tissue is a bit of skin, the patient will live to get that item treated. If the affected parts are big, multifocal, or involve vital organs, the results can be a devastating deprivation of a quality life or even death.

There will always be times when the trauma occurs on the streets, or urgent disease necessitates emergency surgery, before there is any inkling that a pathergy prone condition exists. However, once there is an unexpected or atypical wound complication, that should trigger the relevant work up and indicated treatment. If a patient comes electively and offers a known or suspicious history, then that should be evaluated and confirmed and committed to the active plan of care. Once the presence of these disorders is known, they should or must be treated in advance of surgery using anticoagulants or steroids or both.



Anticoagulants alone can suffice to heal some hypercoagulable wounds, but often that is not enough. Predictably good results come from the "hypercoagulable therapeutic triad" – anticoagulants, hyperbaric oxygen, regenerative biomatrices.

Each item has its role to 1 - arrest pathology (anticoagulants), 2 - restore physiological deficits (hyperbaric oxygen), and 3 - allow healing without risk of wound pathergy (regenerative biomatrices).

This panel has case studies. The focus here is on treatment, but in these cases not just anticoagulants alone, but an effective "therapeutic triad" that consists of anticoagulants, hyperbaric oxygen, and wound closure with regenerative biomatrices.

Left. **67 year old woman.**

History: Acute skin necrosis *(suspicious history).*
No prior risks or history *(no other illness or explanation).*
Exam: Pure thrombo-infarctive pattern *(confirmatory exam).*
Good pulses in feet *(no other illness or explanation).*
Lab: Anti-thrombin-3 deficiency *(confirmatory tests).*
Diagnosis: Anti-thrombin-3 deficiency.
Treatment: Warfarin anticoagulation *(and hyperbaric oxygen, and regenerative biomatrix).*
Outcome: Healed, no recurrence long term on warfarin anticoagulation *(healed with anticoagulation and biomatrix).*

This case illustrates: a spontaneous skin infarction absent any other problem or prior history; characteristic pure thrombo-infarctive pattern of injury without evidence of macro-vascular disease; a lab test confirming a hypercoagulable species (deficiency of an endogenous anticoagulant). Wounds healed (not illustrated) and stable long term, by the combination of anticoagulation plus hyperbaric oxygen plus a regenerative biomatrix.

Center. **44 year old woman.**

History: Achilles tendon rupture, multiple failed surgery, necrosis, ulceration; blind from prior retinal artery occlusion *(suspicious history).*
Otherwise healthy *(no other illness or explanation).*
Lab: Anticardiolipins high, fibrinogen high, periwound TcpO2 low with normal foot and ankle pulses *(confirmatory tests).*
Diagnosis: Antiphospholipid antibody syndrome.
Treatment: Warfarin anticoagulation, then hyperbaric oxygen, then closure with regenerative biomatrix *(hypercoagulable therapeutic triad).*
Outcome: Proper wound behavior only after warfarin, wounds healed *(stable long term).*

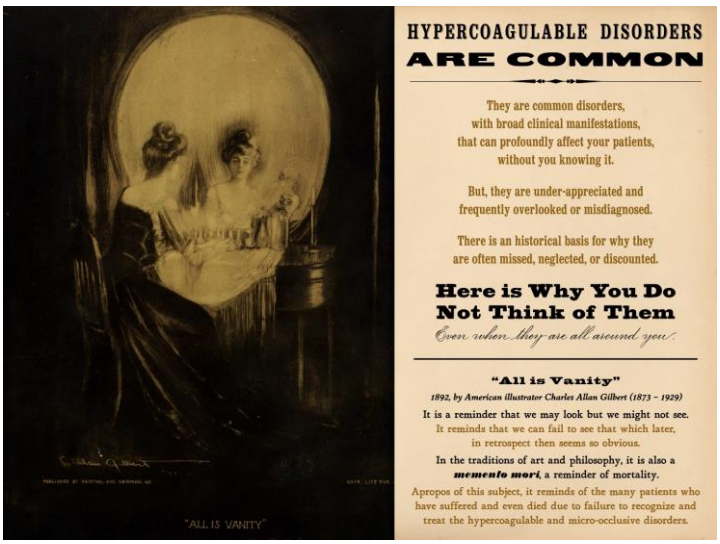
This case illustrates: spontaneous achilles rupture which likely represents chronic weakening from repetitive microtrauma (normal) with reactive microthrombosis (pathological); multiple complications, infarcts, ulcers from multiple operations, persistent skin ulceration; lab tests confirming a hypercoagulable species and local tissue hypoxia in a young person with good pulses. Wounds healed and stable long term, by the combination of anticoagulation to correct the pathology, hyperbaric oxygen to allow revascularization, a regenerative biomatrix to restore normal skin.

Right. 30 year old woman.

History: Refractory active ulcers, severe ischemic pain; prior miscarriage *(suspicious history).*
Multiple DVT but no venous reflux or hypertension *(no other illness or explanation).*
Exam: Mixed inflammatory and ischemic, periwound stasis, wound surface "granulation tissue" infarcts *(confirmatory exam).*
Lab: Lupus anticoagulant, protein C deficiency, periwound TcpO2 low with normal foot and ankle pulses *(confirmatory tests).*
Histology: Diffuse microthrombi in varying stages of consolidation and recanalization *(confirmatory micro-anatomy).*
Diagnosis: Antiphospholipid antibody syndrome, mixed coagulopathy.
Treatment: Warfarin (hard to regulate), then hyperbaric oxygen, then regenerative biomatrix *(hypercoagulable therapeutic triad).*
Outcome: Healed, no recurrence on anticoagulation *(stable long term).*

This case illustrates: severe refractory infarction and ulceration in a young person; lab tests confirming hypercoagulable species, diffuse micro-thrombosis, and local tissue hypoxia in a young person with good pulses. Wounds healed and stable long term, by the combination of anticoagulation, hyperbaric oxygen, and skin restoration with a regenerative biomatrix.

These three cases and others on the preceding panels demonstrate the value of the "hypercoagulable therapeutic triad" – anticoagulants, hyperbaric oxygen, regenerative biomatrices. Each has a physiological and therapeutic role: (1) anticoagulation arrests the primary pathology; (2) hyperbaric oxygen corrects the resulting physiological deficits by permitting neoangiogenic revascularization with in the affected area; (3) the biomatrices allow tissue restoration and healing without risk of wound pathergy. This triad is highly dependable for getting relevant wounds healed. However, the triad need not be applied indiscriminately to all hypercoagulable wounds. Treat only with the modalities required. Anticoagulants are mandatory. Hyperbaric oxygen is for the most severely ischemic wounds. Matrices are used if surgery is needed for essential skin coverage.



21

Hypercoagulable Disorders Are Common

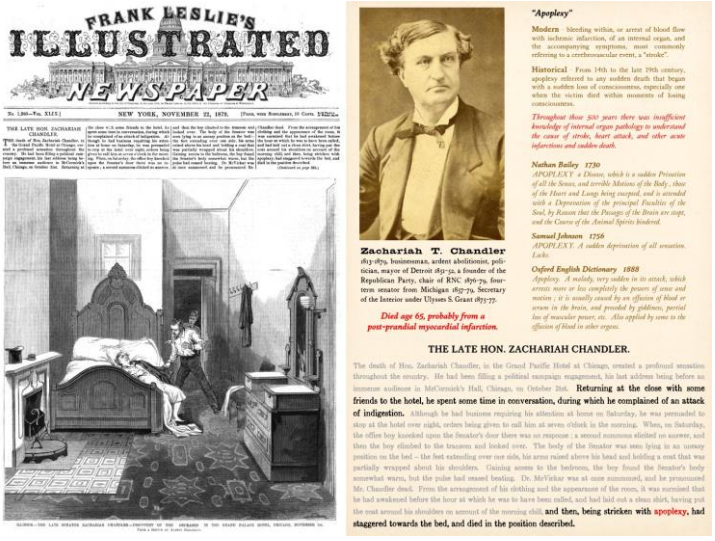
Hypercoagulable disorders and their complications are prevalent and clinically important, but they remain largely under-recognized and often untreated. There are reasons, rooted in medical history and systems physiology, why they are under-appreciated.

There is a dilemma in caring for patients with these disorders. The hypercoagulable disorders remain, among many physicians, largely under-appreciated, overlooked, and misdiagnosed. It was circa 1990 that there was a nascent awareness of them, plus laboratory tests to help support diagnosis. Today, these disorders are more widely appreciated, and so awareness of them, if not familiarity, has improved. Even so, empiric daily experience suggests that more doctors than not will give puzzled looks when mentioning this category of disease or its specific species or disorders. There are also those doctors who are aware of the concept and recognize patients who might be affected, but their workup typically is reduced to a pro forma "coagulation panel" offered by the clinical lab, without awareness of the full spectrum of clinical features or the details of more pointed laboratory diagnosis. Even so, it must be appreciated that these are common disorders. They have broad implications, and they can profoundly affect your patients, oftentimes right under your nose without you knowing it.

If one is unaware of a disorder or disease category, then it is easy to be dismissive of it. The suggestion that such a disorder is actually common may be met with incredulity or even scorn. Yet it was but a century ago that coronary artery thrombosis and myocardial infarction, leading causes of death and disability, and dominant concerns in the medical curriculum and public health care system, were barely known or understood by most physicians (described on the next panel). So, why is it that something prevalent and serious can be perennially under-appreciated and overlooked?

There is an historical basis for this. The following panels survey the history of the coagulopathic disorders and their treatment, wherein are the reasons why today's physician often does not think of these disorders, even when they are all around you.

"All is Vanity" (1892), by American illustrator ***Charles Allan Gilbert*** *(1873 – 1929). A woman at her mirror and makeup table pauses to admire herself. The title is a double entendre, referring to the moralistic theme of the image, but also a reminder that what you might perceive as a human skull is naught but her vanity. Do you see the woman at table or the skull? The image reminds that we may look but we might not see. We might fail to see that which is squarely before us, even if upon later recognition it seems embarrassingly obvious. In the traditions of art and philosophy, this image is considered a* ***memento mori****, a reminder of mortality, in this case the skull warning about the sin of false pride. Apropos of our subject, it reminds of the many patients who have suffered and even died due to failure to recognize and treat hypercoagulable and micro-occlusive disorders.*



22

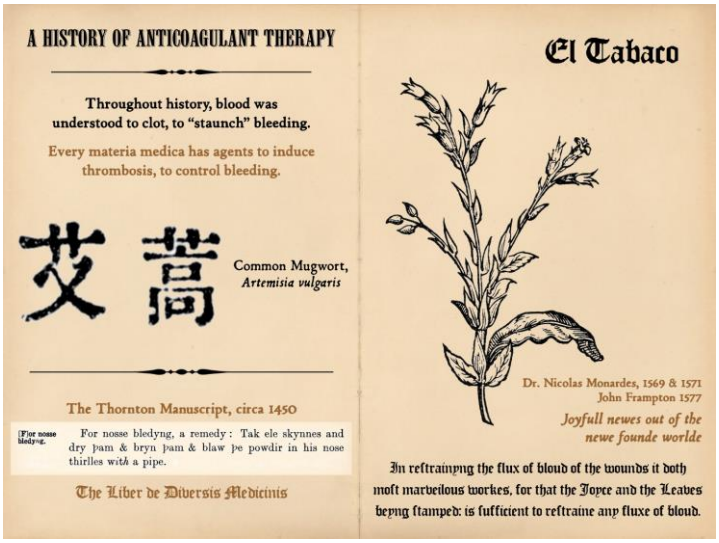
There is no need for anticoagulant therapies if you do not realize that there are hypercoagulable disorders. The clinical need for anti-coagulation is a modern realization. As recently as the latter 19th century, there was no knowledge of such disorders.

In the latter 19th century, America got its graphical news via widely circulated pictorial weeklies and monthlies. Harper's Weekly and Frank Leslie's Illustrated Newspaper were the preeminent of such publications. Illustrated here is the front page of Leslie's issue of November 22, 1879, describing the unexpected sudden death of **Zachariah T. Chandler** (1813-1879). He was a successful business man who became a successful politician and public servant. As an ardent abolitionist, he served as mayor of Detroit (1851-52), then four terms as senator from Michigan (1857-79). He was a founder of the Republican Party, serving as its chair (1876-79). He was also Secretary of the Interior under President Ulysses S. Grant (1875-77). His death therefore was of national importance, deserving of first page status with a nearly full page woodblock illustration. Text on the page reads as follows:

*"***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."*

The Senator, 65 years old, was on the campaign trail, had a busy evening, probably had a big meal, and then complained of indigestion. While we will never know the cause of death with certainty, the story is highly suggestive of a post-prandial myocardial infarction. The newspaper states that he was "stricken with apoplexy". To the modern ear, "apoplexy" implies a stroke, i.e. a cerebrovascular infarct, or else, by extension, a vascular infarct of any other organ. That definition or usage is a modern evolution of the word. The word is in the English lexicon from at least the 14th century, and for 500 years until end of the 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. Nathan Bailey's ***Dictionarium Britannicum*** (1730), one of the first comprehensive dictionaries of the English language, defines the word as *"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's great work, ***A Dictionary of the English Language*** (1756) defines it as *"APOPLEXY. A sudden deprivation of all sensation."* It was only in the mid 1800's that there started to be a certain but still ill defined and incomplete understanding of vascular ischemia and infarction. Thus, the first edition of the ***Oxford English Dictionary*** (1888) defines *"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 modern definition of apoplexy evolved only as the true anatomical and pathophysiological nature of "sudden privation of all the senses" came to be understood. For that half millennium up until the latter 19th century, there was simply insufficient knowledge about physiology and internal organ pathology to understand the cause of stroke, heart attack, and other acute events that result from intravascular coagulation. Until the latter 19th century, there simply was no notion of premorbid or premortal intravascular thrombosis. Thus, no one at that time, in 1879, would have equated Mr. Chandler's "indigestion" with coronary artery thrombosis and myocardial infarction.



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Throughout history, the ill effects of bleeding were obvious, so every culture has a tradition of remedies to promote clotting to stop bleeding. The idea that you might want to inhibit clotting would have been a ludicrous thought in centuries gone by.

The blood coagulation system can malfunction in two ways. (1) It can fail to do its primary function of clotting blood to stop bleeding from injured blood vessels. (2) It can errantly clot within normal blood vessels, thereby arresting blood flow and depriving tissues of life-sustaining circulation. To any modern student or doctor, both problems are freshman knowledge. They might even seem self evident, but that is not true. The idea that blood can clot in normal vessels, depriving organs of flow, is a modern concept, thoroughly non-obvious to pre 20th century scientists. In contrast, throughout history, the fatal consequences of bleeding were overt and obvious. Whether by trauma, accident, war, capital punishment, slaughtering your dinner, and even by surgery, uncontrolled bleeding was a mortal event. Finding ways to staunch or stop bleeding was of paramount concern.

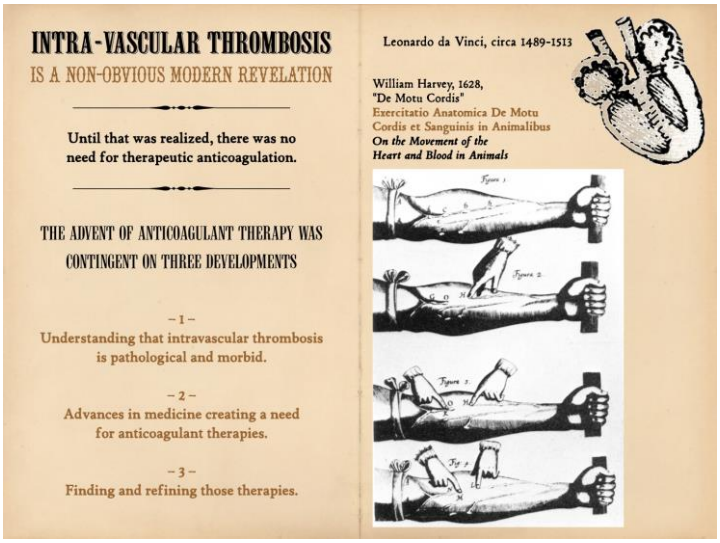
Every culture in the world has a materia medica, the knowledge of how to use plants and other gifts from nature for medicinal purposes. Every materia medica has recipes and remedies to treat mostly any ailment that affects the human condition. This is true for every culture, country, and corner of the world, from neolithic societies to the modern health food store, and from the Chinese apothecary to Granny Clampett and the yarb doctors. Each traditional system of medicine, each of these materias medica, throughout history, has something, often many things, that will control bleeding, be it from wounds or body orifices. Illustrated here are just a few examples of such traditional remedies, treatments meant to arrest the flow of blood out of the body.

Notably absent from the traditional and historical materias medica is anything to "thin" the blood, to prevent clotting. Nothing. I defy you, dear reader, to find an example of such. From a perspective before the 1800's, why would any sane person want to stop coagulation? That would be the same as promoting bleeding. (Deliberate bleeding is of course an historical artifact of pre-scientific medicine up through the mid 19th century. It was done by leeching and by phlebotomy on the barber pole. While mostly ill-conceived and of no value, nonetheless when practiced it was a controlled intervention which is not the same as traumatic or unexpected bleeding. And, of course, the barber or phlebotomist had to ensure that the venotomy stopped bleeding, so those pro-coagulant remedies were important.) For traumatic bleeding, either it stops or you die. It must be stopped by any means. To inhibit clotting would make a wound bleed more, and thus the concept is nonsensical. The notion of therapeutic anticoagulation could only come about once there was an understanding that faulty excessive clotting can in fact occur in certain circumstances, and that illness or death will follow. That realization came only in the latter 19th and early 20th centuries.

The herbaceous plant ***Artemisia vulgaris****, the Common Mugwort (also, Common Wormwood, Chrysanthemum Weed, and others), is a native species through temperate regions of Europe and Asia. It has had many traditional culinary and medicinal uses, including to stop bleeding. In the classic Chinese materia medica, it is known as Ai-Ye or Moxa. Among its many virtues is its ability to stop bleeding, especially menstrual, obstetrical, and gastrointestinal bleeding.*

*One of the gems of medieval British literature and scholarship is the **Thornton Manuscript**. It is MS91 in the Lincoln Cathedral Library. It was penned by **Robert Thornton** (1418-1456), a provincial landowner and amateur scribe who compiled many other works into an anthology of literature and lore. Written 1430-1440, its first of three sections contained romances and other literature. The second has sermons, prayers, and other religious texts. The third is the "Liber de Diversis Medicinis", the Book of Many Remedies, containing botanical and medicinal recipes. For a nose bleed, he records this: "For nosse bledyng, a remedy : Tak ele skynnes and dry þam & bryn þam & blaw þe powdir in his nose thirlles with a pipe." In modern English, it is "For nose bleeding, a remedy: Take eel skins and dry them and burn them and blow the powder in his nostrils with a pipe." (Being in Middle English, note the use of the traditional "þ", thorn, for the "th" sound. The contemporaneous word "thirlle" or "thirl" is a hole or piercing, but "nose thirlles" is cumbersome to pronounce, so it is easy to see how its apostrophic contraction is the etymology of "nostril".)*

***Nicolás Bautista Monardes** (1493-1588) of Seville, Spain, was a physician and naturalist. He wrote a celebrated series of medical books beginning in 1536. Circa 1550 -1570, his focus shifted to the discoveries coming from the trans-Atlantic new world, culminating in his most recognized and influential work. Published in several parts from 1565-1574, the "Historia medicinal de las cosas que se traen de nuestras Indias Occidentales que sirven al uso de la medicina" documents the botanicals and other natural remedies coming from the Americas. It emphasized items of medicinal and potential commercial value. Parts of it were so popular that in 1577 it was translated into English by merchant **John Frampton** under the full title "Ioyfull newes out of the newe founde worlde, wherein is declared the rare and singular vertues of diuerse and sundrie hearbes, trees, oyles, plantes, and stones, with their applications, as well for phisicke as chirurgerie." It is referenced simply as **Joyfull newes out of the newe founde worlde**. Monardes had a fascination with the tobacco plant, not at all surprising as it was the preeminent medicinal herb of the native Americans (shown is Monardes' original illustration of El Tabaco). As part of the native American materia medica, tobacco was 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 marveilous workes, for that the Joyce and the Leaves beyng ſtamped: is ſufficient to reſtraine any fluxe of bloud." ("In restraining the flux of blood of the wounds it does most marvelous works, for that the juice and the leaves being stamped is sufficient to restrain any flux of blood.")*



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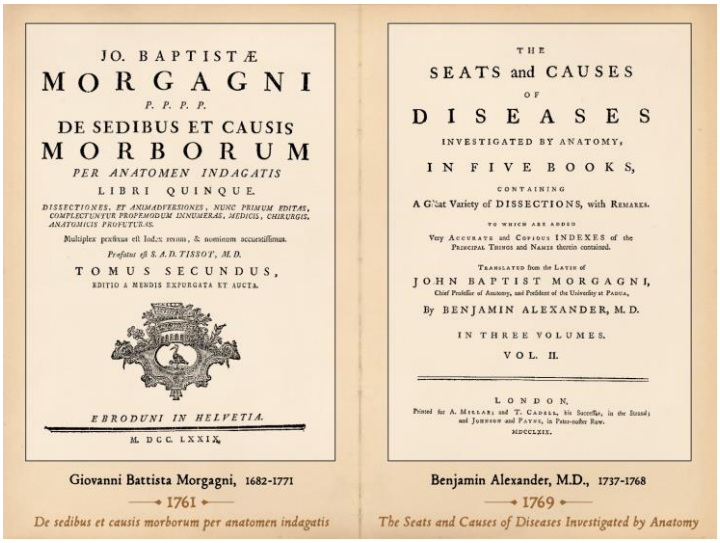
Anticoagulation therapy is predicated on three advances, 1- realization that intravascular thrombosis occurs and is harmful, 2 - the derivative concept that anticoagulant therapies might solve the sequelae of errant thrombosis, 3 - finding and implementing such therapies.

If historically there was no necessity of anticoagulant therapies, then what was the impetus to develop them? Three events had to occur for that to happen. **1 – First** is that there had to be an understanding that intravascular thrombosis actually occurs, and that the consequences are pathological and highly morbid. Only then could the idea of anti-coagulant therapies even be conceptualized. While this is obvious to us today, it was not obvious in the course of medical and scientific history. **2 – Second**, there had to be advances in medicine creating a need for anticoagulant therapies. This started with recognizing, from post-mortem examinations, that in vivo thrombosis does indeed occur. This then had to be correlated with observations in living patients to establish a clinical recognition of the associated signs, symptoms, and progress of such cases creating a foundation for clinical examination and diagnosis. Once you can recognize or diagnose a problem, then you can contemplate treatment. Then, in more modern times, advances in surgery and medical devices furthered the need for anticoagulation. **3 – Third**, theory is fine, but if you do not have a therapeutic tool to treat the newly discovered condition, then you can offer nothing to your patient other than an academic discourse at a most inopportune time in that person's life. Finding and refining anticoagulant therapies was the third contingency of being able to treat these problems.

*Throughout all of history, **Leonardo da Vinci** (1452-1519), probably more so than anyone else, epitomizes the learned man and progressive thinker. Circa 1489-1513, in the Renaissance, as learned men took an interest in biology and human anatomy, da Vinci made thousands of anatomical drawings, including this study of the heart. Most of his drawings were of exceptional detail and accuracy. However, medicine at that time was still mired in medieval and pre-medieval concepts, still overly influenced by the inaccuracies of traditional Galenism. Galen (129-c210) developed principles of physiology and medicine that expanded upon classical concepts from Aristotle and Hippocrates. That system of physiology is predicated on the idea that nutritional intake is constantly converted to body substance with air, chyle, the biles, and heat being shuttled around the body, and with the liver being of central importance. Blood vessels intrinsically pulsate, so the heart, which generates heat, is just part of that cadence. If it sounds convoluted or silly, it is because we know the facts, but back then, they did not. The heart was not understood to move all of the blood. It had a more restricted purpose with respect to the lung and "pneuma", mixing air with blood. During systole, residues from the left ventricle are moved into the pulmonary vein. That of course is backward of the way blood really flows. This then implies that the heart valves were unrecognized or misinterpreted as to function. In his works, da Vinci recognized many things correctly, describing systole and diastole, and even, in some sketches, precisely drawing the cardiac valves. In other sketches though, the valves are trivialized and inaccurate, and he consistently erred in rendering parts of the heart and central vessels (see the illustration). Ultimately, he never recognized the true details of cardiodynamics and how blood circulates. Galenism had held sway over the teaching and practice of medicine throughout the Middle Ages, and that is the philosophy that da Vinci was born into. Thus, in dissecting, examining, and rendering sketches of the heart, even Leonardo brought these erroneous preconceptions to his work. Instead of seeing with his own eyes in this regard, he only saw what the catechism of prior Galenic "knowledge" had taught him to see. True knowledge of the circulation would come more than a century later, with William Harvey.*

William Harvey *(1578-1657), celebrated English physician and physiologist, earned his medical degree at the prestigious University of Padua in 1602 where he studied under the renowned anatomist Hieronymus Fabricius (1537-1619) who in turn had earned his degree at Padua while studying under the equally notable Gabriele Falloppio (1523-1562). Harvey was brilliantly insightful but also doggedly detailed in studying the anatomy and physiology of the blood and circulation in many species. His efforts combined in vivo observations, experiments, and measurements to test lucid hypotheses about the circulation. Through all of this, he came to understand the true nature of circulatory physiology, and the role of the heart, arteries, veins, and their integrated function. He even correctly identified and deduced the purpose of the embryonic ductus arteriosus. The only thing that eluded him were the capillaries. He supported the prevailing view that arteries and veins remained separate, with fluids and blood traversing the tissues in their passage from one side to the other. He can be forgiven inasmuch as he had no microscope for that level of observation (that instrument being invented later, circa 1673 by Antonie van Leeuwenhoek, 1632-1723). Harvey published his magnum opus about the physiology of the circulation in 1628 under the title* ***Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus****, or* ***An Anatomical Exercise on the Motion of the Heart and Blood in Living Beings****, commonly called simply* ***De Motu Cordis****. While there were skeptics and critics at the time, his ideas were appreciated and adopted quickly. The illustration, from De Motu Cordis, shows a simple way to demonstrate the valves and direction of flow in the veins.*

These works of two great thinkers, da Vinci and Harvey, show that conventional teaching can blind one to the truth that is before your eyes, but that an open-minded clean-slate approach to a problem can elucidate the truth. Harvey's work is relevant not solely because he discovered the correct physiology, but because this work established the foundations of experimental physiology. It is this type of inquiring and investigative approach to medical science that ultimately was required to break the shackles of traditional but erroneous thinking and thereby appreciate that blood can clot within living blood vessels, a concept that in Harvey's time remained wholly unobvious and unthought of. There would be many other great medical scientists to follow who also missed this concept, and intravascular thrombosis would not be recognized until three centuries after Harvey.


JO. BAPTISTÆ
MORGAGNI
P. P. P. P.
DE SEDIBUS ET CAUSIS
MORBORUM
PER ANATOMEN INDAGATIS
LIBRI QUINQUE.
DISSECTIONES, ET ANIMADVERSIONES, NUNC PRIMUM EDITAS, COMPLECTUNTUR PROFEMODUM INNUMERAS, MEDICIS, CHIRURGIS, ANATOMICIS PROFUTURAS.
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EBRODUNI IN HELVETIA.
M. DCC. LXXIX.

Giovanni Battista Morgagni, 1682-1771
1761
De sedibus et causis morborum per anatomen indagatis

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,
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MDCCLXIX.

Benjamin Alexander, M.D., 1737-1768
1769
The Seats and Causes of Diseases Investigated by Anatomy

25

The realization that intravascular thrombosis can occur and cause life and limb jeopardy is non-obvious. Every great physiologist and physician-scientist up until the 19th century missed or misunderstood this bit of vital biology and pathology.

The story of ***Giovanni Battista Morgagni***, legendary anatomist and pathologist, further illustrates how intravascular clotting was overlooked and misunderstood. The prestigious University of Padua was founded in 1222. Its medical school and its professors of Anatomy and Surgery were instrumental in advancing knowledge of the human body in the Renaissance and the Age of Reason, leaving a legacy of eponymic anatomical structures, diseases, and therapies that bear their names. Notable names of the chairmen that are still eminently relevant today include Vesalius (1514–1564), Fallopius (1523–1562), Fabricius (1537–1619), Spigelius (1578–1625), along with a host of students and lower rank faculty who also figure prominently in captions of modern anatomy textbooks, including Harvey.

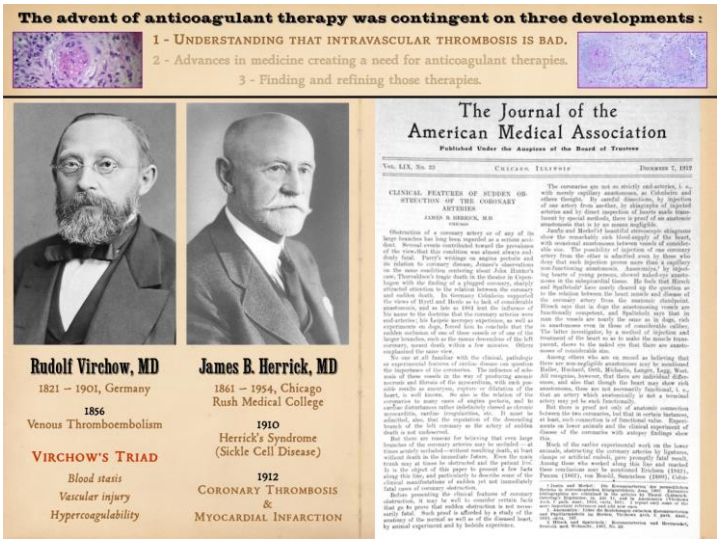
In 1715, Giovanni Battista Morgagni (1682–1771) was promoted from second chair of ordinary theoretical medicine to first chair of anatomy. As the Professor of Anatomy and president of the University at Padua, he had a long and illustrious tenure. His several grand publications were very influential in the progress of medical science and education well into the next century. In 1761, at age 80, he published the epitome of his life's work in the investigative medical sciences, ***De sedibus et causis morborum per anatomen indagatis***. It was his most important and influential work, important enough to be translated quickly into French, German, and English. The English version was translated by Benjamin Alexander, M.D. (1737-1768), published 1769 as ***The Seats and Causes of Diseases Investigated by Anatomy***. Morgagni's stellar contribution was that he took detailed notes of his medical cases, and for patients who died, he correlated post-mortem autopsy findings with pre-mortem medical history. He approached death with the same systematic approach to diagnosis that is done for living patients, and in so doing he could analyze and understand the cause of death. That in turn taught insights into mechanisms of disease and the means of recognizing those diseases by pre-mortem signs and symptoms. He applied the principles of anatomical dissection that his illustrious forebears had used, in trying to discern normal anatomy and physiology, in the interest of understanding morbid conditions. He is the uncontested father of gross pathology, turning pathological anatomy into an exact science.

De sedibus was published in the form of epistles or personal letters to an unidentified friend (a real person or a fictitious rhetorical device is unknown). Seventy such letters were grouped by body part into five books. Each letter has numbered articles, in total 646 anatomical dissections. Each article is 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.

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 it was 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. Furthermore, he did not

understand the atheromas he observed. They are calcific lesions, but they are not bone, and there was no foundation in science at that time to know the difference. 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.

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. But just as Leonardo da Vinci could not see what was directly before him when he looked at the heart, blinded by an inculcated framework of erroneous prior knowledge, so too Morgagni missed some of what we now consider obvious. His great contribution was to understand that each organ is subject to particular diseases, and ever since, organ pathology has been the paradigm of disease. His oversight was to miss the diseases of the general stroma and diffuse infrastructure systems. He might have appreciated these through the microscope, but although it existed by his times, it was not then used in medicine. That would await another century. Why could this highly intelligent and observant man not see what all educated people today take for granted? He had a "hegemonious blindness", ration and reason overruled by erroneous prevailing ideas. When Morgagni looked at coronary thrombosis, he only knew that blood clots in vessels post-mortem, so he could not see that pre-mortem thrombosis had occurred and caused the gross heart changes and death. In Morgagni's day, he did not even have a word for the phenomena, "thrombosis" and "infarction", terms and concepts that would appear only a 100 to 150 years later.



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Realization that intravascular thrombosis occurs and causes recognizable disease is epitomized by Virchow, who elucidated principles of thrombosis, and Herrick, who equated vascular infarction with clinical symptoms and signs, just within the past 100-150 years.

Throughout most of history, intravascular thrombosis was unknown and unthought of, and any speculation on the need for anticoagulant therapies would have been considered insane. The impetus to develop anticoagulants was based on three conceptual and technical advances. (1) There had to be an understanding that intravascular thrombosis actually occurs and is morbid. (2) There had to be advances in clinical medicine to recognize and want to treat thrombosis prone disorders. (3) Treatment would have to be implemented with drugs or other therapies that must be discovered then manufactured. While such concepts seem so basic and obvious to us in the 21st century, the history as presented on the past few panels confirms that these concepts were thoroughly non-obvious and easily overlooked or misunderstood.

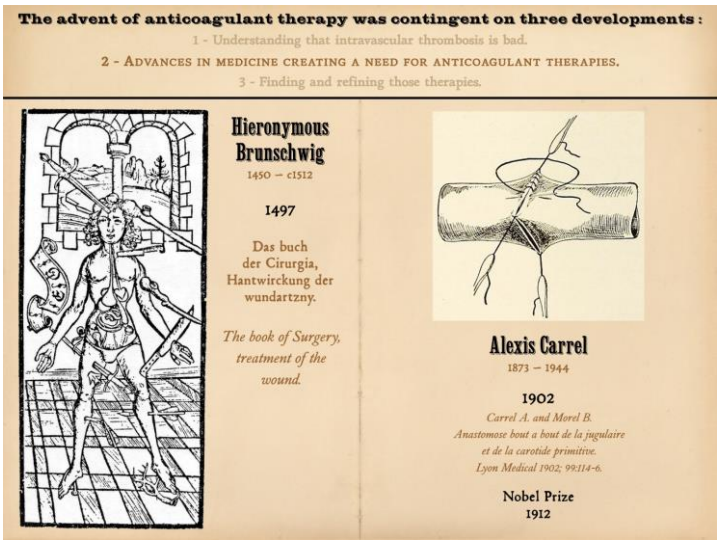
Satisfying Condition 1, that thrombotic disorders are known to occur, did not happen until the 19th century and into the 20th century. We might "bookend" this transmigration of intellectual medical thinking with the contributions of two eminent clinical scientists, ***Rudolf Virchow*** (1821-1901) in Germany, and ***James B. Herrick*** (1861-1954) in the United States.

Rudolf Virchow is best remembered today as the father of histopathology, the microscopic approach to understanding disease, just as a century before Morgagni was celebrated as father of anatomical gross pathology. Virchow established the practice of clinical pathology as we recognize it today, but he also made diverse contributions in many areas of clinical medicine, physiological theory of cell biology, and various topical subjects from cancer to infectious and metabolic diseases. He is considered for example to be the father of public health, for the contributions he made in an 1848 typhus epidemic. In his extensive writings, he greatly enriched the modern medical vocabulary. In 1856, he published ***Collective Treatises on Scientific Medicine*** which included a detailed study of venous thrombosis and pulmonary embolism. He elucidated a concept that we now see as so basic, but which was not at all understood back then when clots were found in the pulmonary arteries on post-mortem examination. In his astute analysis of the pathophysiology, he introduced the words "thrombosis" and "embolism". He also hypothesized how intravenous clotting could be triggered in peripheral veins, elucidating three conditions that could induce intravascular thrombosis, what we know today as ***Virchow's Triad*** (although that term did not appear in texts until a century later, circa 1950): clotting can occur due to alterations of vessels making them thrombogenic, altered hemodynamics creating low flow or stasis of blood in the vessels, and heightened thrombogenicity of the blood itself. The idea of hypercoagulability was thus posited as theory, although it would again be another 100-150 years before we would discover and systematize actual hypercoagulable disorders. With this seminal 1856 contribution, the concept of ante-mortem vascular thrombosis was firmly established. However, aside from now understanding the pathogenesis of the disorder, there was still no way to recognize, except by autopsy, that a sudden apoplexy was due to pulmonary embolism, nor were other thrombo-infarctive disorders such as myocardial infarction yet understood or equated with intravascular thrombosis. Nonetheless, Virchow's contribution opened minds and investigative medicine to the possibility.

James B. Herrick, MD, lived his life in the Chicago area. He attended medical school at Rush Medical College, interned at Cook County Hospital, and eventually served as professor at Rush 1900-1927, practicing medicine until 1945. In 1910 he peered through the microscope at the blood smear of an ill medical student who was from Grenada. What he observed and published was long known as Herrick's Syndrome, called today by its pathological name, sickle cell disease. He made his second landmark contribution to the medical sciences and literature in 1912. He published in JAMA, the Journal of the American Medical Association, a paper titled ***"Clinical Features of Sudden Obstruction of the Coronary Arteries"***. Angina pectoris was clearly elucidated in 1772 as a defined clinical syndrome, including its crescendo to sudden death, by William Heberden (1710-1801). Subsequent to that, other insightful researchers deduced or discovered some aspect of angina pectoris that related it to the heart, myocardial energy demands, and blood supply and the coronary arteries. Notable figures were Caleb Hillier Parry (1755-1822) and Edward Jenner (1749-1823), whom Herrick referenced. Herrick also makes note of *"Thorvaldsen's tragic death in the theater in Copenhagen with the finding of a*

plugged coronary artery, sharply attracted attention to the relation between the coronary artery and sudden death." Bertel Thorvaldsen (1770-1844) was an internationally acclaimed Danish sculptor. Just as Zachariah T. Chandler had died from an apoplexy after a busy day and a large dinner, so too Thorvaldsen died suddenly at the Copenhagen Royal Theatre after a dinner with friends. An autopsy was done which showed coronary artery thrombosis. Herrick also cites anatomical research in the latter 19th century trying to understand coronary artery anatomy and answer questions about arterial collateralization. It would seem that all of the elements of understanding myocardial infarction were there by the turn of the 20th century, but no one had actually yet associated all of these ideas into a cohesive concept of clinically recognizable and treatable disease. That is what Herrick did in 1912. Through an analysis of known cardiac science and correlation with patient profiles, Herrick clarified that angina pectoris and myocardial infarction are complications of the coronary arteries, that angina per se and even coronary thrombosis are not always fatal, that thrombotic occlusion is the cause of death for those who die, and that angina and related pre-fatal symptoms can be recognized as the clinical signs and syndrome of coronary artery occlusion. People can have atheromatous disease of the coronary arteries with angina, and then those arteries can clot and cause infarction, and the problem or pending problem can be diagnosed while the patient is still alive.

Between Virchow in 1856 explaining the nature of intravascular venous thrombosis, then Herrick in 1912 clarifying the clinical presentation of coronary artery thrombosis, medical science and clinical practice had finally come to understand that pre-mortem intravascular thrombosis can occur, that it can be fatal, and that the clinical manifestations can be recognized. **Condition 1** of the road to anticoagulant therapies has now been satisfied. Next, how does medicine respond to these newly appreciated medical problems, to develop concepts of clinical diagnosis and care (Condition 2), and then develop tools or technologies to treat them to save a life or a limb (Condition 3)?



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Clinical need for anticoagulants, even though they did not exist then, arose in the early 20th century from efforts to prevent or treat the newly appreciated thrombotic conditions. This included technical advances such as the Nobel worthy advent of surgery on blood vessels.

The year 1912, when Herrick published his landmark paper, was also notable for the Nobel Prize in medicine, given to ***Alexis Carrel, M.D.*** (1873-1944) for developing the surgical techniques that allowed blood vessels to be repaired and organs to be transplanted. This was a technical advancement in medical science quite different than the pathological concerns of Virchow and Herrick, but they all had the common theme of injured and altered blood vessels and the risk of blood flowing within them to clot.

Carrel was raised and educated in France, then migrated to Canada and then the United States in 1903, eventually in 1906 joining New York's Rockefeller Institute of Medical Research where he spent the rest of his career. He had a formative experience as a young surgeon when, in 1894, the French President was assassinated by stabbing, bleeding to death from a portal vein injury. The event inspired Carrel to develop techniques of repairing blood vessels. He developed comprehensive approaches to the problem, allowing for the suture and repair of arteries, veins, and grafts, even developing the technical details of organ transplantation.

Clinically, Carrel's contributions had an impact in military and even civilian practice, allowing vascular injuries to be repaired, thereby saving lives and avoiding amputations. However, dedicated attention to vascular surgery, especially as a defined discipline with a focus on reconstruction of congenital, acquired, and degenerative vascular diseases, and on clinical organ transplantation, was still four decades away after his Nobel Prize. For elective reconstructive vascular surgery, relevant concepts of vascular pathology, clinical diagnosis, and technical support were not yet conceived in 1912. Practical allogeneic organ transplantation was also dependent on solving problems of cross-individual immunity. The prototype procedures of elective vascular surgery, the aortic aneurysm, the aortic or aorto-bifemoral bypass, the femoro-popliteal bypass, the coronary artery bypass, the dialysis access fistula, renal transplantation, and portacaval shunts were first done in the late 1940's through 1960. These in turn depended on parallel technologies such as heart bypass, renal dialysis, and immunosuppression. Of further vital importance, dependable oral anticoagulant drugs appeared contemporaneously in the 1950's. However, in the first half of the 20th century, the focus on vascular surgery was on basic repair techniques, and there was a corollary to manipulating and suturing blood vessels – they can clot in the process. Note that none of these developments implicated an abnormal, heightened, exaggerated, or pathological form of thrombosis. Clotting was assumed to be normal, with thrombosis of normal blood being triggered by the low flows or altered vessels of trauma or atherosclerosis. Appreciation that there are actual hyperthrombotic disorders that can clot despite normal flows or vessels would not come about until circa 1990.

In the world of surgery, concerns about blood have traditionally focused on bleeding. Whether surgeons treat trauma where bleeding is caused by the injury, or else surgeons contend with the bleeding they make by their own incisions, bleeding is a potentially fatal concern, so it must be controlled or stopped. The contributions of Carrel revealed a previously unknown facet of surgery that forever altered the surgeon's relationship to blood and bleeding – the need to avoid or prevent thrombosis. With the awareness of intravascular thrombosis revealed by Virchow and Herrick and the need to translate that knowledge into effective clinical practice meant to save lives, and with the technical developments of Carrel that promised to save lives after trauma or other vascular and non-vascular disease, the world of medicine now had an appreciation of thrombotic disease and complications along with nascent concepts about how to care for the patients and the problems. Beginning circa 1912 with Herrick and Carrel, and continuing on for another half century, **Condition 2** of the road to anticoagulant therapies was satisfied. The next step would be to develop effective treatments to prevent or reverse or otherwise contend with intravascular thrombosis.

In the 15th century, surgeons concerned themselves with bleeding in that they had to stop it. The cause of bleeding was often trauma, as illustrated. Johannes Gutenberg (c1400-1468) is famous as the inventor of moveable type and the printing press. His first small works were printed circa 1450, and his magnificent 42-line bible, the famous "Gutenberg Bible" taken as the landmark start of printed books, was published 1455. It was not long afterward in Germany that printed books began to appear on many and diverse subjects, including the first printed textbooks of medicine and surgery. One such book was ***Das buch der Cirurgia, Hantwirckung der Wundartzny****, (1497, The Book of Surgery, Handiwork of the Wound Doctor) by* ***Hieronymous Brunschwig*** *(c1450 – c1512), a lifelong military and wound surgeon from Strasbourg. 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. This book compiled ancient and medieval knowledge with Brunschwig's own experience. Later and more prominent books, such as* ***Hans von Gersdorff's*** *(c1455-c1529)* ***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. In the time of Brunschwig and von Gersdorff, blood vessels and bleeding got the attention of surgeons in order to stop the bleeding.*

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.

Although several incidental vascular operations were reported in the last decade of the 19th century, it was in 1902 that a highly influential work appeared that changed surgical practice. It was ***Anastomose bout a bout de la jugulaire et de la carotide primitive****, (End to end anastomosis of the jugular and primitive [common] carotid) by A. Carrel and B. Morel in the Lyon Medical journal. Shown is Alexis Carrel's illustration of his "triangulation technique" that was essential in assuring a competent and patent anastomosis. From there into the early years of limited vascular surgery, and then through the development of Vascular Surgery as a defined discipline beginning circa 1950, managing thrombosis has been integrally bound to vascular surgery for nearly 100 years. Anticoagulant therapies have been a part of the art for nearly 80 years, but it is only in the past 20 years that we have realized that intrinsic coagulation abnormalities can subvert the best vascular operations or ordinary efforts to modulate blood clotting.*

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To treat thrombosis with anticoagulants requires that one have such pharmaceuticals. However, traditional materias medica, having only had agents to promote clotting rather than prevent it, were unable to satisfy the needs for this conceptual new class of agents.

The third contingency of anticoagulant therapies was the ability to find pharmaceuticals that might inhibit or retard clot formation in order to keep blood flowing through vessels. To appreciate how this came about, it is important to understand the origins of pharmaceuticals throughout history. A scientific understanding of chemistry started in the latter 1700's, and by the mid 19th century, chemical knowledge was relatively robust including the early understanding of organic and even biological chemistry. An infrastructure of chemical manufacturing developed due to the success of the aniline dye industry. The active compounds in medicinal plants could be extracted, purified, and even analyzed for chemical structure, and pharmaceutical companies were offering many of these as purified versions of traditional remedies. By end of the century, the infrastructure was there to be able to manufacture synthesized pharmaceuticals. The first of these was aspirin, acetylsalicylic acid, a laboratory derivative of naturally occurring plant derived salicylic. Production and sale of aspirin started in 1899 by the Bayer company. In the meantime, chemists at universities and pharmaceutical companies were engaged in trying to elucidate as much knowledge as possible about the chemistry and metabolic pathways of life, partly out of pure academic interest, partly to further the healing arts, and partly to find medicinal items of commercial value.

Prior to aspirin, medications were derived from nature. Modern physicians might dismiss or trivialize what they pejoratively perceive as "herbal medicines", but until the 19th century, there were no other sources of therapeutic chemicals. Prestigious physicians and surgeons of prior eras were the academics and knowledge keepers about medical botany and pharmaceutical practice. Surgeons were often the herbarists to the Crown and superintendents of the royal gardens wherein the knowledge and supply of medicines was preserved. The great herbals of the 16th through 18th centuries were often masterpieces of scholarly work, the printer's arts, medicinal knowledge, and cultural wisdom, and they served as the pharmacy textbooks of their days. They had many vulnerary drugs (botanicals and recipes) to heal wounds, and remedies to staunch bleeding. As already observed though, the materias medica of the world had no remedies to promote bleeding or thin the blood because the concept of such a thing was irrational, unnecessary, and dangerous.

Notice how the advent of chemical physiology with the support of university research and education, the advent of pharmaceutical chemistry and manufacturing, and the discoveries about intravascular thrombosis were all occurring simultaneously, circa 1850 through 1920. That era saw the progress from first insights about morbid clotting to clinical recognition of the illnesses and rational concepts about possible treatments. However, "possible treatments" was just an ill-defined hypothetical wishlist. The problem was that if you want to seek an anticoagulant, where do you turn to? There is no prior knowledge of such a thing. The traditional materias medica have no candidates. What we do have in that era are well funded universities and chemical manufacturers with sophisticated chemistry labs that can study biological chemistry. Anticoagulants were going to come from new discoveries, not the old pharmacopœias. With no prior knowledge of what an anticoagulant might "look like" with respect to source or chemical structure, the discoveries not surprisingly came by serendipity.

***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 are the ephemeral documentation of a once flourishing patent medicine trade during the latter 19th century. Concurrently, the legitimate ethical scientific drug industry was arising. 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 Food and Drug Administration. 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.*

*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*

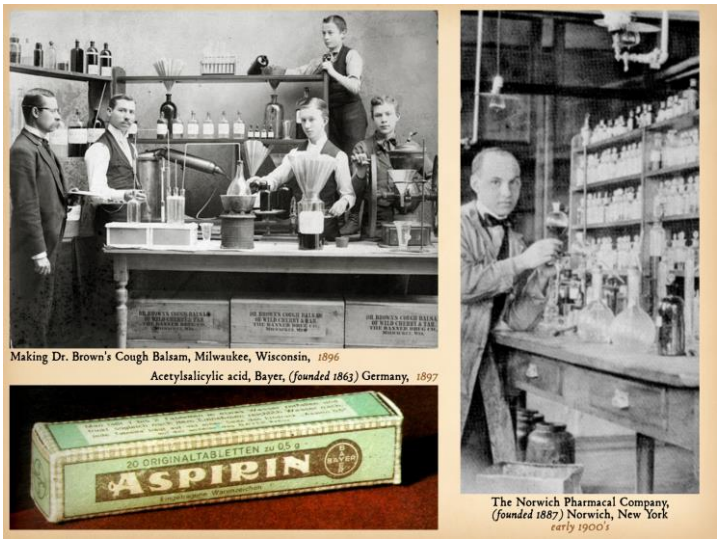
The mid 16th through the 17th centuries, the epitome of the renaissance that founded our principles of scientific thought, investigation, and education, was also the era of the great herbals. While some of these botanical encyclopedias were written by "naturalists", most were written by physicians, because these were the pharmacopœias of the time. Remember that the first commercial synthetic drug was aspirin in 1899, 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.

*Concerning medicinal agents for surgical purposes, stopping bleeding and healing wounds are the two primary intents. During the era when pharmacists compounded the doctor's often elaborate prescription, mullein was a common vulnerary, an ingredient for wounds and 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. Hypercoagulability is an area that has lagged behind in clinical appreciation throughout history. Thus, there are no traditional remedies for the problem, but this also means that hypercoagulability has been spared the nonsense and silliness of ersatz patent medicines. As we learn more about these disorders, we can keep an open mind to new pharmaceuticals of legitimate merit.*

If you are interested in medicinal history, in general or related to surgery and wounds, more information is at the following links, panels 12 – 16:

http://www.arimedica.com/content/arimedica_integrating%20new%20products_gottlieb-me_2009-0926.pdf
http://www.arimedica.com/content/arimedica_integrating%20new%20products_gottlieb-me_annotated.pdf



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A scientific pharmaceutical industry arose in the latter 19th century. While those companies did not seek or invent anticoagulants, they created a scientific, technical, and manufacturing infrastructure that allowed future such drugs to be studied and developed.

This panel continues the theme of the last one about the progression of pharmaceutical science. It was circa the turn of the 20th century that we had developed a robust and dependable ability to find, study, purify, then manufacture new drugs. The scientific, academic, technical, and industrial infrastructure necessary to do this were fully established by the time that the first two contingencies of anticoagulant therapies had been satisfied – knowing that morbid intravascular coagulation occurs, and that there is a clinical need to correct these problems. The intellectual and technical basis was now established to satisfy the third contingency, to find actual anticoagulant therapies. The illustrations on this panel document the environment in which these pending discoveries would happen.

*Shown is an image of making **Dr. Brown's Cough Balsam** in Milwaukee, Wisconsin, 1896. This was the tail end of the patent medicine era. What they were making was not a precision pharmaceutical, but it served its purpose for symptomatic relief, and as such it is what today would be an over-the-counter non-prescription item. The paper box with the **Bayer** company logo (founded 1863) sold **Aspirin**, acetylsalicylic acid, that industrially produced variation of the natural salicylic acid, first sold 1899. "Aspirin" was the commercial trade name for the product. As part of Germany's reparations after World War I, various intellectual properties were made public, including Aspirin, after which the name was adopted as an official chemical name. Also shown is a scientist circa 1900 at the **Norwich Pharmacal Company**, founded 1887 in Norwich, New York, and later known as Norwich Pharmaceutical Company then Norwich Eaton Pharmaceuticals. Its first important product introduced 1893 was Unguentine the first pre-packaged antiseptic surgical dressing.*

These photos were taken at the midpoint of a golden century of biochemistry. In 1828, ***Friedrich Wöhler*** (1800-1882) synthesized urea. In 1858 ***Friedrich August Kekulé*** (1829-1896) understood the nature of carbon tetravalency, and then in 1865 he understood the benzene ring. These events are symbolic markers of the advent of biological chemistry. ***James Watson*** (1928-) and ***Francis Crick*** (1916-2004) and their discovery in 1953 of DNA structure 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 redefined all of science. 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 ones shown, in universities and pharmaceutical companies, and still do, to understand how our molecules work. The main sequence of the plasma protein coagulation system was largely pieced together by the end of that golden century. And in the middle, just after turn of the century, all of the elements were there to discover the first anticoagulant, in time to serve the nascent demand for such.

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The First Anticoagulant – Heparin

The first anticoagulant discovered, developed, and put into clinical service was heparin. It was discovered purely by serendipity and happenstance, a fascinating historical saga that began 1916, culminating in the first clinical paper on therapeutic anticoagulation in 1937.

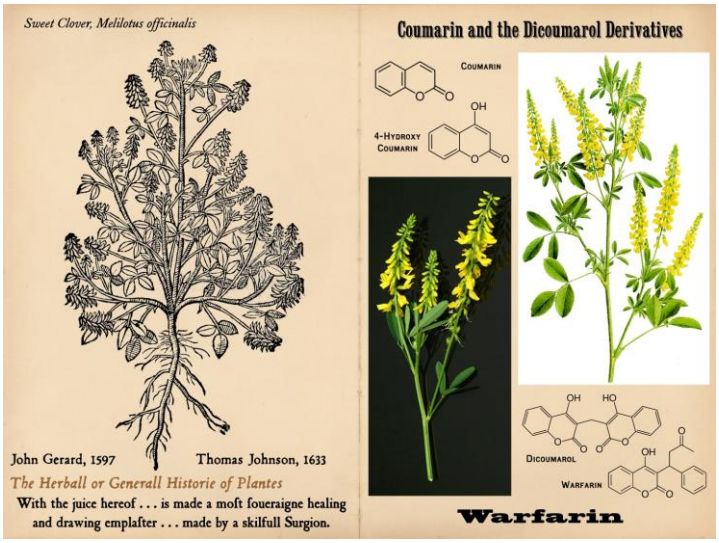
The first anticoagulant was heparin. It was an accidental discovery in 1916, made while looking for something else, but it was not discovered "in a vacuum". Enough was already known about the coagulation system to permit the research that coincidentally discovered it. In the mid 19th century, the observation was made that tissues contained a factor that would trigger blood to clot. In 1905, ***Paul Oskar Morawitz*** (1879-1936), a student at University of Tubingen, was studying this "tissue factor" (his term for this procoagulant property was "thrombokinase"). He went on to propose the first meaningful and fundamentally valid theory of blood coagulation based on four essential components: thrombokinase, calcium, prothrombin, and fibrinogen. TF-thrombokinase is now called tissue thromboplastin or factor III, the activation agent for the extrinsic clotting pathway. The dates show that by the early years of the 20th century, biological chemistry and physiology were already rather sophisticated, and that quite a bit was known about the chemistry of coagulation.

In 1916, ***Jay McLean*** (1890-1957) was a sophomore medical student at the Johns Hopkins Medical School. He was working in the lab of prominent physiologist ***William Henry Howell*** (1860-1945). (*Pictured is an anonymous medical student at Hopkins circa 1915. The insets are portraits of Howell and McLean.*) McLean was doing a project to identify tissue thromboplastins, in the interest of an ever greater understanding of coagulation.

Instead, he identified a tissue anticoagulant. Being especially abundant in the liver, he called it "***heparin***". Because of the recent work of Herrick, Carrel, and others, 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. By this time, there was considerable interest in developing heparin as a pharmaceutical, but making a safe product proved rather non-trivial.

Credit for working out a safe source of heparin goes to Canadian ***Charles Best*** (1899-1978). Best is best remembered for his work with ***Frederick Banting*** (1891-1941) to discover and isolate insulin from the pancreas, and to help develop methods suitable for its large scale pharmaceutical production. Insulin was introduced into clinical service in 1923 by the Eli Lilly Company under the trade name Iletin. (*Pictured are Banting and Best in 1921 on the roof of their research building with their mascot and lab partner in whom the insulin was tested.*) From about 1929 through 1937, Best and colleagues identified the lung and other organs as richer safer sources of heparin. 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 use was by Swedish surgeon ***Clarence Crafoord*** (1899-1984), published in *Acta Chirurgica Scandinavica* in 1937, for the prevention of venous thrombosis after surgery.

Condition 3 of the road to anticoagulant therapies was now satisfied, and the world had its first anticoagulant medication, heparin. Concurrently, myocardial infarction had entered medical textbooks as standard clinical knowledge. There was increasing interest in operating on diseased blood vessels throughout the body. There was also growing interest in trying to operate in nature's last holdout against the surgeon, the chest and its most vital organs. Development of all of this stalled somewhat in the coming decade as the world went to war. However, following World War II, there was an explosion of technical developments in surgery which, as described in panels above, led to the development of sophisticated procedures in heart and vascular surgery, endovascular implants, and long term catheters and fistulas. None of this would have moved beyond a hypothetical or conceptual stage were it not for heparin, the miracle tool that could prevent clotting and keep such surgery safe and effective.



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The Second Anticoagulant – The Dicoumarol Derivatives

Chapter two in the anticoagulant drug story is "coumarin and warfarin", another tale of serendipity, inquisitive minds, and the benefits of an academic-industrial approach to medical development, thereby giving us options to adapt treatment to individual needs.

The road to anticoagulant therapies has two more chapters. As crucial as heparin was for keeping patients and surgery safe, it had its limitations. It was mainly administered intravenously. It was too big a molecule to have dependable absorption given subcutaneously. An oral form was not possible. This meant that anticoagulation could not be administered for outpatients and long term use. Also, it was not a benign drug to use. It had a narrow therapeutic index, and out-of-range dosing on either side was potentially fatal, from clotting or from bleeding. However, finding the proper effective or toxic dose could be quite hit or miss, and variable from one to another patient. Also, being from xenogeneic cross-species sources, it could incite allergy or resistance, making it dangerous or ineffective. An alternative was needed for long term and outpatient use. And, a method was needed to measure its effect and gauge proper dosage, person by person. Two developments satisfied these needs. The dicoumarol drugs were discovered in the 1920's, and by the 1950's they had been developed into useable pharmaceuticals. Electronic and precision manufacturing technologies derived from the war found their way into civilian and medical products, giving us automated laboratory equipment that could do rapid and reliable tests to properly regulate therapy.

*Pictured is **Melilotus officinalis**, one of the **Sweet Clovers**, also known as melilot. Native to temperate parts of Europe and Asia, it has been naturalized to many parts of the world, primarily as a forage plant for cattle. It has a notable place in the ancient materias medica, with a variety of therapeutic properties. Its medicinal properties were described by the ancient Greek herbalist **Pedanius Dioscorides** (c40-c90), and by surgeon **John Gerard** (1545-1612) in his famous 1597 Herball (see Panel 28 above) and again in its celebrated 1633 revision by botanist **Thomas Johnson** (c1595-1644). **The Herball or Generall Historie of Plantes** has a thorough explanation of the sweet clover (its beautiful woodcut is shown) including its uses as an anti-inflammatory and wound healing agent:*

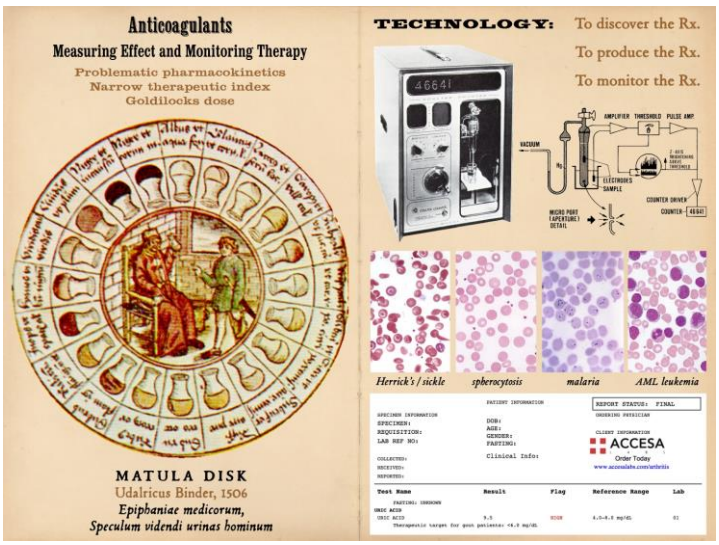
With the juice hereof . . . is made a moft foueraigne healing and drawing emplafter . . . made by a skilfull Surgion.

In the 1920's in the northwest United States and adjacent parts of Canada, cattle started dying from a bleeding disorder, either spontaneously or after procedures like castrating bulls. The problem was investigated, and it was tracked to improperly cured sweet clover hay. The melilot has a characteristic sweet odor, known in the flavor and fragrance industry as the odor of "new-mown hay". The odor comes from the chemical coumarin. "Sweet clover disease" happened due to seasonal circumstances that kept the hay from being fried fully, allowing fungus to affect it. Those were the Great Depression years, and farmers could not afford to throw the moldy hay away, but feeding it to the cattle obviously poisoned them. A clue was that the bad hay had turned bitter, and that was tracked to a fungus induced chemical change in the coumarin to bishydroxycoumarin. Also known as ***dicoumarol***, it was finally identified and synthesized in the early 1940's in the laboratory of Karl Paul Link (1901-1978) at the University of Wisconsin. 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.

Dicoumarol proved difficult to use because it too had problematic pharmacokinetics and a narrow therapeutic index. Regulating doses and therapy were difficult, and suitable clinical tests that could quantify coagulation were not yet established. However, there was faith in the value of the chemical, so considerable effort was put into variations of the chemistry and tests to monitor therapy. Approximately a hundred derivatives of the molecule were synthesized and tested. It turned out that the anticoagulant effects, as a vitamin K inhibitor, appeared when coumarin was hydroxylated at the 4-position. That chemical, 4-hydroxy coumarin, found commercial success as a rat poison. Of the few versions that made their way to clinical practice, the one that prevailed was ***warfarin*** (named for the sponsor of its research and development, the Wisconsin Alumni Research Foundation). 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" had proven to be the most practical way of monitoring therapy with the coumarin derivatives, and now there was a pragmatic way to measure and monitor therapy.

Imagine what would have happened had sick cows been a problem a century earlier, in the 1820's. Investigative science would probably have deduced easily enough that moldy hay was the problem. It might have been an instructive lesson in food and farming safety, but that is all. Abnormal bleeding was known to be bad, and this would have simply reinforced that understanding. Nothing more would have come from the experience, since nobody would have had a state of mind or frame of reference that said, "Inhibits clotting, just what we've been looking for !" However, there were profound changes over the next 100 years: the advent of scientific chemistry, organic chemistry, pharmaceutical science and manufacturing, biochemistry and chemical physiology, mapping of much of the plasma coagulation pathway, and profound insights into thrombotic and vascular diseases. Thus, by the 1920's, there was enough knowledge of the subject that the value of an anticoagulant could be recognized. At that time, there was only one anticoagulant, heparin. It was not yet in clinical use, and thus still unknown to rank and file physicians, but the profession was primed to take note of promising news. Louis Pasteur (1822-1895), the famous French microbiologist, and a contemporary of Rudolf Virchow, stated in a lecture in 1854 *"Dans les champs de l'observation le hasard ne favorise que les esprits préparés." ("In the fields of observation, chance favors only the prepared mind.")* It is commonly restated as *"Chance favors the prepared mind"*, and that is the story of the coumarin drugs. It is interesting to speculate that had the cows gotten sick in the 1820's, that lessons would have been learned about animal feeds, then the escapade relegated to dusty reports and forgotten history, the lucky chance to find dicoumarol retired and gone.

Contingency 1 –> Contingency 2 –> Contingency 3 –> Problem solved. It was at that point, circa 1960, that our modern concepts of short and long term anticoagulation with heparin and individualized dicoumarol or warfarin dosing were established. It was at that point that the medical arts and sciences had fully prevailed in understanding basic coagulation, errant coagulation within vessels, how to recognize the clinical disorders and complications, and how to treat them. However, there is yet another chapter that was unseen and unaccounted for in 1960, the hypercoagulable disorders. This was the concept that when blood clotted inside blood vessels, it was not always a response to injury or thrombogenic vessels, but rather an innate imbalance or abnormality of the coagulation system itself. That domain of knowledge would not arise until circa 1990.



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Anticoagulants – Measuring Effect and Monitoring Therapy

Heparin and especially dicoumarol's have odd pharmacokinetics and narrow therapeutic indices making them erratic and dangerous. Safe and effective use requires laboratory monitoring. Until that could be done, circa 1960, these drugs were of restricted benefit.

In this history of anticoagulation, it is now circa 1950 – 1960. We have a detailed understanding of circulatory and thrombotic physiology and pathology, a robust appreciation of the clinical presentation of thrombotic and occlusive disorders, sound concepts for treating such illnesses, and nascent surgical technologies for correcting diseased vascular structures. (The first open heart operation, 1953, and the defining procedures of vascular surgery such as coronary artery bypass, aortic replacement, and femoropopliteal bypass were all reported in this decade.) In addition to now treating natural thrombotic conditions, we are also discovering that the new operations and vascular implants also need the benefits of anticoagulation. Fortunately, we now have two classes of drugs useful for anticoagulation, the heparins and the dicoumarol derivatives. But, there is a problem, the inconsistencies and dangers of using these anticoagulants. How can we maximize their therapeutic usefulness to prevent errant thrombosis while minimizing the sometimes disastrous side effects of unintended bleeding?

Both drugs have virtues and problems. Heparin, used intravenously, has a short half life and predictable pharmacokinetics, but its bioactivity varies from person to person, so dosing must be individualized. The oral dicoumarol drugs have odd pharmacokinetics plus a long serum half-life and long time constant of biological effect, likewise requiring individual dosing. Both have narrow therapeutic indices (toxic dose divided by effective dose). This all means that using these drugs can be erratic and dangerous, either inadequate therapeutic effect leading to clots that were meant to be prevented, or else unintended over-anticoagulation causing bleeding. How then can the level or effect of these drugs be monitored to keep serum concentration in a proper range?

Laboratory tests were required to satisfy this need, to monitor and regulate therapy. By this time, numerous laboratory tests were extant to measure parameters of the coagulation system, most derived from basic science investigations, but with many adapted to the clinical lab. At that time though, clinical tests were not automated, so an intern or medical student or technician had to perform the studies which of necessity could not be overly laborious or finicky. Furthermore, most coagulation tests were designed to measure specific components or branches of the coagulation system, and since the anticoagulant drugs affected different parts of the thrombotic system, there was no such thing as a generic coagulation test. Eventually, two tests were validated as useful. Quick's prothrombin time (PT) was developed in 1935 (the INR normalization was

introduced in 1980). The activated partial thromboplastin time (aPTT) was developed in 1953. Testing and clinical studies showed that best safety, efficacy, and clinical correlation came from using the aPTT to regulate heparin therapy, and the PT or PT-inr was best suited for warfarin and the dicoumarol drugs. However, theory and science aside, if a test is too cumbersome to perform, or too laborious and time consuming for the lab staff or the beleaguered intern, then it is likely to be ignored. The salvation of the intern and the rise of clinical lab tests were a consequence of machines that appeared in the 1950's, the chemistry and hematology auto-analyzers. The hematology autoanalyzer was developed by Wallace Coulter and introduced into service circa 1957. The SMA (sequential multiple analysis) machine was introduced within a year to do serum chemistry (the SMA-6 and -12 are now called the BMP and CMP, basic and comprehensive metabolic panels). 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." Many other machines followed to automate clinical testing, including coagulation assays. Once such tests were readily available, heparin and warfarin could be used safely. This in turn lead to greater development of vascular and heart surgery, endovascular implants, dialysis and catheter technologies, and interventional vascular procedures.

Beginning in the 1910's, technology allowed us to identify chemicals that could be used as anticoagulants. Then, technology allowed us to purify and manufacture those therapies. Then, technology developed modalities to monitor therapy in the lab. The benefits of that technology now continue. ***The clinical lab has been beneficial to the recognition and appreciation of hypercoagulable disorders and states***, allowing for easy diagnosis and treatment monitoring. Without the lab tests that let us look at a broad spectrum of possible pro-thrombotic species, we would not be certain about the diagnosis in many patients. The pentad Hypercoagulable Syndrome and wound exam and histology would still be diagnostic for many patients, but it is always easier to be certain about the diagnosis when a quantifiable marker of the disease can be measured. Furthermore, ready availability of coagulation assays allows anticoagulant drugs to be used safely, long term and as an outpatient.

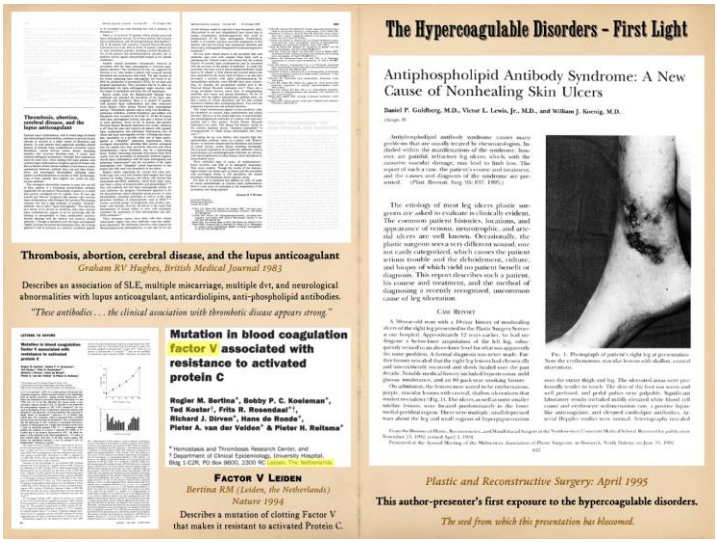
However, the ready availability of clinical chemistry tests has also had in some ways a detrimental effect on recognition of hypercoagulable disorders. While we can ever more readily measure individual species in the blood, there is no single test that by itself says "hypercoagulability". If we, as doctors, get ever more dependent on the lab to identify disease by the variance of a lab test, while we fail to recognize the syndromic features of a complex disorder or understand its complex pathophysiology, then we will fail to diagnose correctly. This is especially true when the lab tests can have relevant variations in both directions, and a cluster of tests must be considered as an ensemble. This was alluded to on *Panel 12* under *3-C Differential Dx*. ". . . there is nothing like the distinctive histology or lab studies that establish diagnoses such as sickle cell disease or thalassemia or spherocytosis which are also micro-occlusive disorders that cause chronic ulcers and wound pathergy. Therein is one of the reasons why the hypercoagulable disorders remain underappreciated – the diagnosis cannot be defined or pinned down by a single test or metabolic interaction, and thus the syndrome and physiology are hard to clarify. . . . Not having anything of that certainty in the realm of hypercoagulability has made it historically hard to even crystallize the concept let alone commit it to textbooks and student teaching."

Hypercoagulable chemicals can be detected in the lab, but hypercoagulable disorders and states cannot be diagnosed in the lab. If you are waiting for "the answer" in a single test, you will not find it. They are diagnosed based on history, physical, lab, and histology, all in coordination with sequential observations, responses to treatment, and knowledge about coagulation pathophysiology.

*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. They were illustrated by woodblock engraving, then printed on a press, and for the more prestigious and expensive works they could be 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. To diagnose diabetes, 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 pertinent as they are today. Illustrated is Wallace Coulter's "electrical particle counter for blood cells". It has been the standard method of analyzing the hemogram ever since, being supplanted only recently by laser cytometry methods. the diagram illustrates how it works. The sample goes into a basin in which hangs a glass tube with a micron scale perforation. Negative suction on the tube draws sample fluid through the hole, while electrodes on either side measure electrical impedance. Since cells with their lipid membranes are good insulators, when they squirm through the channel they change the electrical values across that gap. Size of the signal corresponds to size of the particle crossing the gap, meaning that leukocytes, erythrocytes, and platelets can be discriminated. By drawing fluid at a regulated rate. e.g., microliters per second, and electronically counting the signal spikes in a given time, the absolute number of cells per mm^3 can be measured.

Illustrated is a laboratory report showing a high uric acid indicative of gout. The microscope slides show blood smears diagnostic for sickle disease (Herrick's syndrome), spherocytosis, malaria (Plasmodium falciparum bodies seen in the cells), and acute myelogenous leukemia. In these examples, one test yields a definitive diagnosis of a distinct, well-defined, well known nosological entity or "named disease". There is nothing quite so singularly pathognomonic for identifying and diagnosing a hypercoagulable state.



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The Hypercoagulable Disorders – First Light

Intravascular clotting is an interplay between blood and vessels, and by 1960 we had conquered those elements related to vessels and blood flow. The third element, inherent hypercoagulability of the blood, was still an undiscovered hypothesis, but that changed circa 1985-1995.

In 1856, Virchow posited a theory of abnormal intravascular thrombosis depended on three factors - the condition of the blood vessels, the flow characteristics of blood moving through those vessels, and the inherent coagulation potential of the blood. The process might be likened to a bit of terpsichore. The vessels are one partner, the blood is the other, and the flow is the dance that engages them. By the 1960's, we had come to understand the thrombogenicity of abnormal blood vessels and of altered blood flow. We had developed sound principles and methods of treating thrombosis due to aberrant vessels and flow, principles that remain today the foundations of cardiovascular surgery and anti-thrombotic treatments. However, the third element, conditions of the blood that would make it intrinsically prone to clot within vessels, a condition of "hypercoagulability", was still unknown.

The theory is sound, rather obvious in principle, but no clinical conditions had been identified. Telling a patient "I must put you on a blood thinner" because your blood vessels are diseased, or because we are about to do a vascular operation or arrest the circulation, or because there is an artificial blood vessel in you now, that makes sense. Telling a patient the same because they just had a potentially life threatening pulmonary embolism or exercise induced thrombosis of the subclavian vein (Paget-Schroetter syndrome), that makes sense. But to suggest that one must take anticoagulants when there is no disorder of the blood vessels or blood flow, absent any overt history of thrombosis, that would have made no sense. To suggest that you will be treated with anticoagulants because you had a miscarriage or because you have rheumatoid arthritis or multiple sclerosis or because your surgical incision fell apart, that would have been derided as pretentious insanity.

Lupus, including systemic lupus erythematosus and variants, has been recognized vaguely as a disease for a long time. The name "lupus" is attributed to ***Roggerio dei Frugardi*** (c1140-c1195) commonly known as Rogerius, a surgeon from Salerno. He was memorable for having written the first great textbook of surgery adopted and influential through all of Europe, ***Practica Chirurgiae*** (c1170-1180), also called ***Chirurgiae Magistri Rogerii***, *"The Surgery of Master Rogerius"*. The term lupus was used because the facial lesions that were part of the disorder were reminiscent of a wolf bite. The name is also attributed to acclaimed French dermatologist ***Pierre Cazenave*** (1795-1877) who discriminated the erythematosus type as *lupus érythèmateux*. A modern systematic and pathological approach to the disease began in 1872 when Hungarian dermatologist ***Moritz Kaposi*** (1837-1902) identified systemic lupus, with its many constitutional features, as distinct from cutaneous lupus. Two other men are credited with completing the gross clinical and pathological recognition of the disease, Polish-German dermatologist ***Josef Jadassohn*** (1863-1936) and Canadian-American ***William Osler*** (1849-1919) who described the visceral involvements of the disease in the early years of the 20th century. Contemporaneously, it was being reported that patients who had the clinical features of systemic lupus often had a false reactivity to the VDRL syphilis test, an indication that immunity played some role in lupus. However, a pathophysiological and etiological concept of the disease would not come until mid century. That is when, in 1948, hematologist ***Malcolm Hargraves*** (1904-1981) et al in Minnesota discovered the LE cell in bone marrow. LE cells are phagocytes containing the nuclei or nuclear material of other cells. That is the basis of anti-nuclear autoimmunization. By the 1950's, there were clinical lab tests for antinuclear antibodies. Another crucial contemporaneous development in that 1940-1950 period was from New York pathologist ***Paul Klemperer*** (1887-1964). His landmark 1942 paper in JAMA, titled "*Acute disseminated lupus erythematosus and diffuse scleroderma*" coined the term "collagen disease". His introductory paragraph is noteworthy: "*The thesis of Morgagni that diseases reside in certain organs of the human body has dominated pathological anatomy and clinical investigation for centuries. Every diagnostic endeavor was directed toward establishing the fundamental organ disease. No doubt, this working hypothesis has been the cornerstone on which rests the edifice of modern medicine. . . . Nevertheless, one cannot justly maintain that an essential site is established in every disease.*" Morgagni had also failed to see that there are diffuse infrastructure disorders in the body, diseases of the general stroma, but Klemperer had now given them a name and an impetus for further study. Also, in 1950, **Philip Showalter Hench** (1896-1965) and colleagues were awarded the Nobel Prize for Physiology or Medicine for discovering cortisone and its use in treating rheumatoid arthritis. Thus, by 1960, just as with our new comprehensive appreciation of vascular diseases, we now had an integrated understanding of the autoimmune basis for a diffuse disorder of the connective tissue stroma, plus tools for confirming the diagnosis, and a crucial drug to effectively suppress inflammation and immunity, and thereby treat a class of diseases which are of crippling and often lethal significance.

The association of the connective tissue disorders and autoimmunity with blood and coagulation came about surreptitiously and quietly, with incidental papers reported here and there that failed to connect into a larger comprehensive picture until circa 1990. The presence of serum anticoagulants and various phospholipids and an association with lupus were described in the first half of the 20th century. A few fascinating papers appeared with clues about hypercoagulability: ***(1) Gitlow S, Goldmark C. Generalized capillary and arteriolar thrombosis: Report of two cases with a discussion of the literature.*** Annals of Internal Medicine, 1939. *"These two cases are being reported together because they show similar pathologic changes even though clinically they differ entirely. The pathologic process is characterized by generalized arteriolar and capillary thrombosis. . . . [conditions] resembling lupus erythematosus"*; ***(2) Moschcowitz E. An acute febrile pleiochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries - An undescribed disease.*** Archives of Internal Medicine, 1925. The Moschcowitz paper was considered important enough that, as interest in lupus and autoimmunity and collagen diseases and steroids was arising, it was reprinted in The American Journal of Medicine in 1952. For the next 30 years, there continued to be a smattering of papers on lupus and immunity and phospholipids and

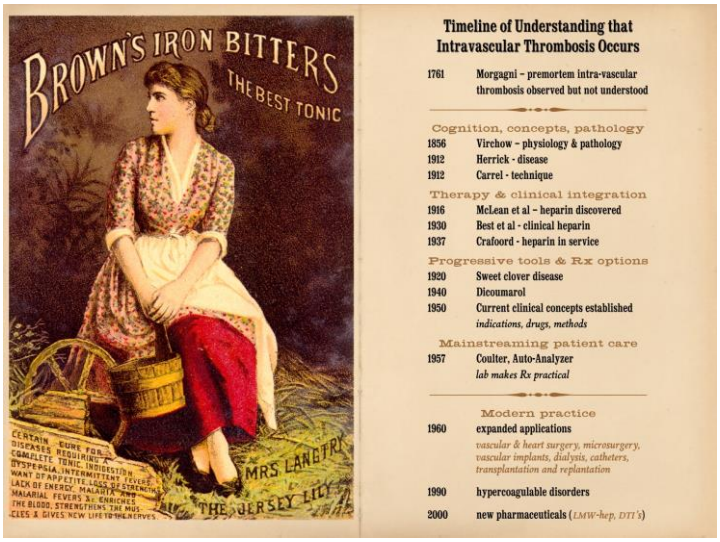
coagulation that all touched on the subject of hypercoagulability, but as with the proverbial "blind men and the elephant", each saw just a parochial piece of the big picture, never the entirety.

Pictured here are landmark papers. First is by **Graham RV Hughes**, published in the British Medical Journal, 1983. ***Thrombosis, abortion, cerebral disease, and the lupus anticoagulant*** describes a syndromic of systemic lupus erythematosus, multiple miscarriage, multiple deep venous thrombosis, and neurological abnormalities associated with lupus anticoagulant, anticardiolipins, anti-phospholipid antibodies. Hughes concludes that *"These antibodies . . . the clinical association with thrombotic disease appears strong."* It is notable because it finally amalgamated multiple threads of interest into a cohesive concept about a common clinical presentation. This paper is generally cited as the switch that turned on interest in hypercoagulability. The focus being on an autoimmune disorder, ***it identified immune procoagulants as the hypercoagulable species***. The disorder took on the names ***anticardiolipin syndrome*** and ***antiphospholipid antibody syndrome***. These names required nomenclature reconciliation with the actual immune chemistry, and by the mid 1990's, APL or APLA, antiphospholipid antibody syndrome prevailed.

In this same era, interest in the plasma clotting system had by now identified the natural endogenous anticoagulants, proteins C & S and the antithrombins. Activated Protein C (APC, activated by binding to protein S) is one of the prime regulators, decelerators, of thrombosis. It works by binding to and thus inhibiting factor V. If factor V is resistant to APC, it is disinhibited, causing unfettered conversion of prothrombin to thrombin, thus a hypercoagulable condition. In 1994, the journal Nature published ***Mutation in blood coagulation factor V associated with resistance to activated protein C*** by ***RM Bertina*** et al. This was an inborn mutation that prevented APC from binding to factor V. It proved to be both common in the population and potent in its pro-thrombotic effects, as stated by the authors *"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, protein S, antithrombin deficiency) together."* The work having been done at Leiden University Medical Center in the Netherlands, the mutant gene, known officially as Factor V Leiden rs6025 or R506Q, took the common name of ***Factor V Leiden***. This paper resulted in the general awareness and interest in the prime sequence ***plasma protein hypercoagulopathies, the thrombophilic disorders***.

By the time of the Bertina paper, there was worldwide interest in understanding these problems. Hundreds or thousands of papers have since been published that describe immunochemistry, demographics, and clinical features. Of interest is that many papers describe microthrombosis in various organs and tissues, and associate the chemical species with a multitude of classic nosological entities from rheumatoid to multiple sclerosis, but none necessarily describe an integrated theory of general hypercoagulability. Because so many observant authors have documented the association of these disorders with organs or tissues or other disorders of their respective interests or specialties, you, the reader, can find a paper on almost any organ or entity that has felt the sting of the hypercoagulopathies. That includes wounds and ulcers, and other soft tissue pathologies. This author-presenter had his first introduction to the problem with the paper illustrated. It appeared April, 1995 in *Plastic and Reconstructive Surgery*, ***Goldberg DP, Lewis VL, Koenig WJ. Antiphospholipid Antibody Syndrome: A New Cause of Nonhealing Skin Ulcers.*** This paper was the original seed from which this presentation has ultimately blossomed.

Because these disorders have been of interest since the 1980 - 1990's, and because there are so many documentary reports, it would stand to reason that these disorders are now firmly entrenched in the minds of physicians, that clinical manifestations would be readily recognized, that treatment principles would be clearly understood, and that they would be well represented on the pages of standard textbooks or in medical or specialty curricula and board exams, but that does not appear to be the case. Despite that these disorders are one of the most common causes of chronic and non-healing wounds, most practitioners of the new specialty of Wounds seem to be unaware of these disorders. This foray into medical history was instigated by the premise that the hypercoagulable disorders are not as well appreciated as they should be. The following panel summarizes this essay, and tries to draw conclusions about the historical basis for this deficiency, an historical scotoma that has blinded medicine to these rather prevalent and extremely morbid and important diseases.



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Since the 1960's, anticoagulation has been mainstream. Three further advances have occurred, 1- expanded uses from medical technologies, 2- appreciation of hypercoagulable disorders, and 3 - newer classes of drugs. Knowledge of these conditions is still young.

This panel summarizes the history so far presented, how we came from no knowledge whatsoever about intravascular thrombosis to sound clinical practices for such problems in the span of about 150 years. This history ends circa 1960, when we have heparin and warfarin to treat our patients. The further history is that of the hypercoagulable disorders, the chapter we ourselves are now living through beginning circa 1990.

Timeline of Understanding that Intravascular Thrombosis Occurs

1761 Morgagni – premortem intra-vascular thrombosis observed but not understood. He saw the atheromas and the myocardial infarction, but he thought the clots were post-mortem grume.

Cognition, concepts, pathology

1856 Virchow – physiology & pathology. He understood thrombosis and embolism, establishing physiological principles about coagulation.
1912 Herrick – disease. In recognizing the signs & symptoms of coronary occlusion, he established clinicopathological correlation of disease.
1912 Carrel – technique. In developing surgical methods for blood vessels, he created a technical need for anticoagulant therapies.

Therapy & clinical integration

1916 McLean et al – heparin discovered. Accidental discovery of an anticoagulant was recognized useful for the new found medical conditions.
1930 Best et al - clinical heparin. The laboratory discovery of heparin needed substantial development to make it clinically useful.
1937 Crafoord - heparin in service. Once available, heparin proved its worth, to prevent post-operative deep vein thrombosis.

Progressive tools & Rx options

1920 Sweet clover disease. Evaluation of a strange cattle ailment led to discovery of the second class of anticoagulant drugs.
1940 Dicoumarol. Refinement of the sweet clover chemical led to clinically useful drugs.
1950 Current clinical concepts established. These include the anticoagulant drugs, their indications, and methods of administration & safe use.

Mainstreaming patient care

1957 Coulter, Auto-Analyzer. The chemical autoanalyzers allowed blood testing to be done easily, making specialized treatments practical.

Modern practice

1960 Expanded applications. Anticoagulation has allowed development of new and progressive surgery: vascular & heart surgery, microsurgery, vascular implants, dialysis, catheters, transplantation and replantation
1990 Hypercoagulable disorders. An awareness that hypercoagulable disorders exist, and that their clinical sequelae can be recognized.
2000 New pharmaceuticals. This allow greater safety and utility in managing patients: low MW heparins, hirudins, direct thrombin inhibitors.

Pictured is a trade card from the patent medicine era, circa 1885-1890. It is for Brown's Iron Bitters, made by the Brown Chemical Company, Baltimore. It features the image of the Emilie Charlotte Langtry (née Le Breton, 1853 -1929), known popularly as Lillie (or Lily) Langtry and nicknamed "The Jersey Lily". She was a British-American socialite and actress. As a stage actress, she was a bona fide celebrity superstar of her day, lest you think that celebrity endorsements and name-dropping salesmanship are something new. Concerning the Iron Bitters, it should be good for the blood, and indeed the script states "enriches the blood" along with a long list of putative virtues. It is included here for no special reason – it just looked good.

Why the Hypercoagulable Disorders are not Given the Attention They Warrant

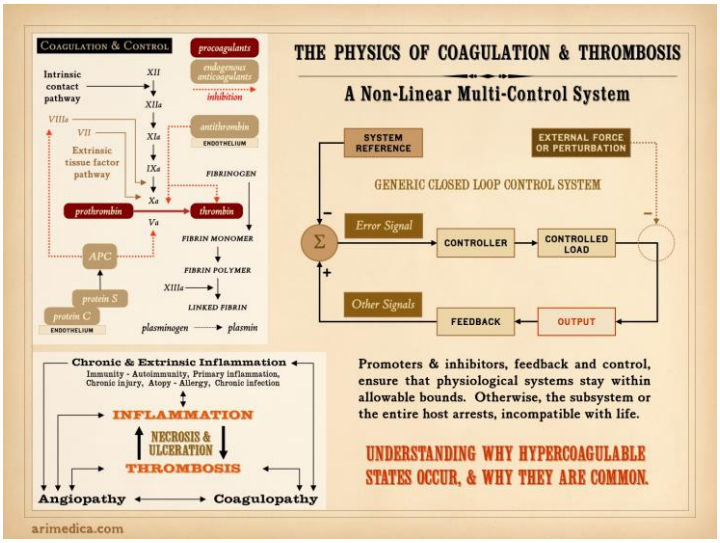
This essay strives to explain why modern clinical medicine lags in its appreciation of hypercoagulable disorders, even though so much of the relevant physiology is known in great detail. There are two broad reasons, **(1) the historical scotoma**, and **(2) the 19th century holdover of seeing physiology in strictly linear terms**. That second item will be explored in the following panels. Here though we can summarize the first part. We fail to see them because there is an historical scotoma, a blind spot in an otherwise clear vision of human biology and blood clotting physiology. Leonardo da Vinci could not see the valves of the heart for what they were because his Galenist heritage held too much sway over even his intellect. The same was true for Morgagni who stared directly at thrombosis, and although he correctly discerned almost all other diseases, he could not break loose from his innate knowledge that what he saw could not happen, thus he did not see it. Even as Virchow correctly explained the nature of intravascular venous thrombosis, he could not extrapolate that to any clinical correlation about errant thrombosis in general. Only in 1912 was James Herrick able, finally, to correlate this concept of pathological physiology with clinical presentation. The coordinated picture of errant intravascular thrombosis causing ischemic infarction with recognizable signs and symptoms is thus just a century old. Over the past century, much of the clinical, technical, and commercial development devoted to this subject has focused on methods of treating clots once they happen, and mainly for the overt and dramatic macro-vascular events where technical intervention is more exciting and beguiling than understanding the pathophysiology and prevention of arcane and confusing chronic problems.

Throughout history, there was never a concept of hypercoagulability. To suggest that physicians, who must stop bleeding, might need an anticoagulant would have been insanity if not heresy. After Herrick and Carrel and the realization that anticoagulation would serve a purpose, it was not easy to find such drugs. The utter absence of prior art and science meant that our only two drugs were discovered by sheer luck, one by a medical student doing the opposite research in a university lab, and the other by destitute Depression era farmers. The story is too strange to be fiction. Students and young doctors today, learning their craft in a modern hospital, are exposed endlessly to the complications of bleeding and hypocoagulation (due to hemorrhage, transfusion, hypothermia, sepsis, liver disease, etc.). Hypercoagulability in contrast is often slow, insidious, and chronic, never revealing its microthrombi directly to the naked eye or the bedside exam. Even when the disease exerts its worst effects and causes death, it does so stealthily, never revealing to naive eyes the weapon that it used. It becomes all too easy to focus on one of the prominent signs or symptoms and ascribe a common diagnosis to it, rather than analyze the broad spectrum of features to find the syndromic diagnosis.

Modern hospital and technical practices have introduced other distractions from proper and insightful diagnosis. There is often too much focus on looking for convenient tokenized diagnoses based on a lab test that has varied this way or that way. Diagnosis is easy when all we need do is look at the laboratory slip or imaging then state "hyperkalemia" or "hyper-parathormone" or "mitral regurgitation". For the hypercoagulable disorders, this is not so easy, sometimes confusing. High protein C and low protein C both mean hypercoagulability, but for different reasons, which makes interpretation seem difficult if you are not familiar with these tests. Factor V Leiden implies hypercoagulability, but the contrapositive "not hypercoagulable implies not V Leiden" is not true, because people can have the gene but not always be in a hypercoagulable state. If you learned that prothrombin gene mutation or lupus anticoagulant causes hypercoagulability, but not the full spectrum of the disorder, then it is easy to misinterpret various coagulation tests. Even with comprehensive knowledge, the diagnosis is not revealed by a single value, rather by an integrated understanding of several or many such tests. A such, these diseases are unlike many of the problems we encounter and diagnose, making it too easy to forget them or ignore them in favor of more practical or mono-parameter diagnoses.

The problem is compounded when the diseases and diagnoses are eschewed or ignored by patients and physicians. Some of the case histories presented here mention that the patients lapsed in taking their warfarin. The problem is no different than those who stop taking their blood pressure or diabetes pills – they are feeling better so perceive no value in taking them, or they get bored or lazy about it. The problem is worse though when other physicians ignore or fail to understand the diagnosis or anticoagulant treatment and stop it. It could be a surgeon worried that

being on anticoagulants will cause bleeding. It could be anyone, not getting a full history from the patient, and assuming that the problem is nonexistent or irrelevant. At the time that this presentation was delivered, year 2018, this remains a regular occurrence in our practice and for our patients, even with the necessary medical records and means of professional communication being freely available. However, that so many doctors do not understand or appreciate the hypercoagulable problems can be forgiven, because the subject seems to be greatly ignored in the medical curriculum, as evidenced by students' class notes and reading assignments, lecture topics, and chapters in textbooks. The historical lack of appreciation, the diverse and protean manifestations that can all too easily be confused with other organ-specific diagnoses, the subtlety or quietude of the disease, and its sometimes confusing diagnostic criteria keep it off the map, the agenda, the curriculum. Until at least one generation of young physicians learns to understand and recognize the problem in its various manifestations, it will remain "below the radar".



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The Physics of Coagulation and Thrombosis

The other broad reason that hypercoagulability is misunderstood is that, not only is it often clinically occult and non-obvious, but physiologically it is variable in expression and behavior. Why this is so is rooted in the physics of complex dynamical systems.

This panel explains why coagulation is a non-linear multi-control system. This is rooted in the complex feedbacks and dependencies of the normal coagulation system. Hyper-thrombosis is an exaggerated state that arises in the non-linearities of the inflammation-thrombosis interdependencies. Understanding the non-linear dynamical basis of coagulation leads to an appreciation that hypercoagulable states can not only occur but are expected to be common.

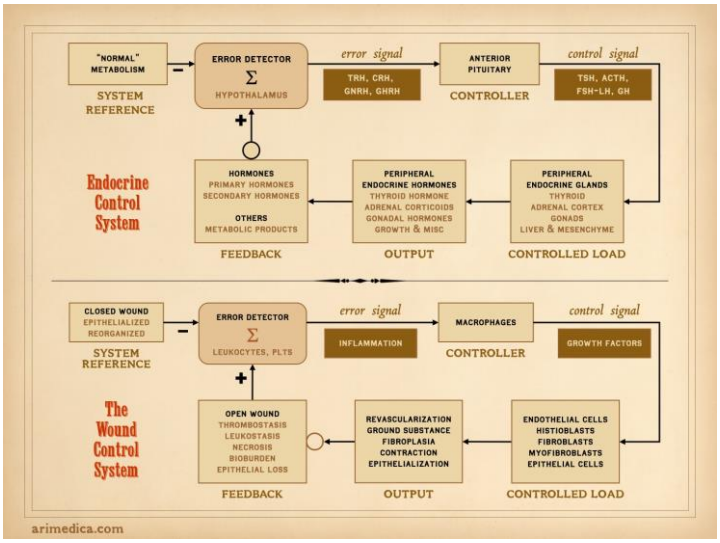
What does that mean? Coagulation is a complex system having a dozen or so main sequence proteins, many potent cofactors, and untold lesser cofactors and intermediaries all interacting. If any one parameter gets too far out of bounds, there needs to be a way to boost it up or reel it back in order to stay in its effective operating range (physiological systems that saturate or extinguish are generally morbid or dead). This idea of regulation or control depends on feedback, being able to sense where the system is at any moment, so that adjustments can be made back toward the center line. In physiology, nearly all systems and elements have promoters and inhibitors so that bipolar control can be exerted, actively pushing or pulling a given species in either direction as required. Any system that uses feedback, senses its current state to adjust its future state, is "non-linear". When many factors are interoperating and mutually regulating, it is a multi-control system. Coagulation is thus a physiological non-linear multi-control system. It is balanced or tuned, has a "system reference", that ensures it does not trigger and clot within normal vessels, but does so readily upon exposure to non vessel materials. The miracle of it is that it reliably keep its tune, its balance, its control on the centerline, not misbehaving when things are healthy, but coming to the rescue when there is an injury. But, being so complex, things can understandably go awry.

To understand why, exam a generalized closed loop control system. **Reference:** This is the target or value that the system is meant to be at, that the control loop works to maintain. **Nodes:** These are combinatorial points that yield values. The main node, indicated as a "summation point", is a comparator where the difference between the ***system state*** and the ***system reference*** is monitored. **Error signal:** This is the output of the primary summation point, indicating variances of the system away from the reference value. **Controller:** This is the component that is directly influenced by the error signal, the first part of the mechanism needed to implement corrections. It is like the executive or general that receives all of the intelligence from the field then must issue orders to the troops to take some action. **Load:** This is the element acted on by the controller, the actual productive machinery which will change the system state and try to correct the system error. These are the employees or troops who, commanded by the controller, do the real work of creating the company output. **Output:** This is the productive output of the controlled load, that which modifies the state of the system, bringing the system back toward the system reference. **Feedback:** Some method is needed to measure the current state of the system and report that back to the comparator node. **Forces:** Extrinsic to the control loop itself, these are applied stresses or perturbations which alter the state of the system, forcing a response from the control loop to try to restore the reference state. They can sum into the loop at nodes which, depending on the specific nature of the system, can be located almost anywhere on the loop. **Control Loop:** There is no start or stop, no on-off switch. As long as the system as a whole is "on" and active, the control loop is free running, always striving to restore the system to its reference value. If the reference value is reached, then the output of the main node is zero, and there is no force driving the loop. If there is any intrinsic decay or drift in the state of the system, or any perturbation due to extrinsic stresses, then the compared value is no longer zero, and an error signal is generated and the loop is driven. Nearly all physiological systems work this way.

A key feature of non-linear multi-control systems is that they tend to be chaotic. "Chaos" in this sense is a technical term, not the layman's sense of crazy or disordered. The concept means that although a parameter will stay within its operating bounds, it might not have a predictable trajectory or pattern within that space. These terms and the behaviors of dynamical (time evolving) systems are explained on a following panel. If you could focus on a single coagulation species, e.g. plasma fibrinogen, and measure its concentration continuously and with sufficient precision, it is not going to have a precise invariant value. Even with good control, its level will be high and low, but on average on its center value, with its ups and downs within certain small bounds. However, this degree of good control is contingent on the proper tuning and dynamics of each of its elements, and if any one or many get disordered, good control can get stressed and eventually fail. Likewise, if extrinsic stresses or perturbations over tax the ability of the system to respond and control, it can fail. For coagulation, potent effects of inflammation, autoimmunity, and altered vessels and flow can overwhelm the system. If the system fails low, bleeding is a risk. If the system fails high, errant thrombosis is the risk.

You can start to see here why altered coagulation dynamics have the potential to be common. With so many levels of control and interaction, many stresses on or within the system can be absorbed and the "ship righted". However, with so many items, there is greater likelihood of one getting

offset or broken, meaning that other elements will have already compensated, perhaps close to their limit of response. Then, when one more stress comes along, "the straw that breaks the camels back", the perturbation exceeds the limits of the controller or controlled load to respond. The system ramps up or ramps down out of bounds, and the health of the system fails. You can also see here why people with intrinsic hypercoagulable disorders, such as one of the gene mutations, are not always in a hypercoagulable state. If the system is healthy enough, one errant item or stress cannot swamp the system if control is otherwise good, but there will be little latitude or leeway for further perturbation or imbalance.



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Control Loops in Physiological Systems

Complex systems have feedbacks, promoters and inhibitors, amplifiers and attenuators, and other dynamical elements which all interact with each other. Multi-control systems of this nature abound in the body - essentially all physiological systems are such.

Feedback, control, and non-linearity are inherent in all physiological systems. This is essential so that no system exceeds operational limits. Medical students often learn about feedback by studying the endocrine system, but all physiological systems qualify and can be modeled as such. To illustrate physiological control systems, this panel will show how the Endocrine System can be parsed into the various control and feedback elements. The same analysis is then applied to the Wound, the biology of repair after injury. The coagulation system, with its many layers of control and interaction, cannot be so readily diagramed, but it follows similar principles and organization. If the idea of control in physiological systems seems unfamiliar to you, it reflects a legacy of "old biology", so first, here is an essay on systems physiology, old and new.

For conventional biosciences in the 20th century, "system" implied cardiovascular or gastrointestinal or musculoskeletal. Feedback and control infrequently found a place in the big metabolic charts which were generally presented as one way linear processes. This is because biological science, systematology, and academics beginning in the latter 19th century were indelibly colored by the science and discoveries of those times when chemistry, organic chemistry, and a scientific pharmaceutical industry turned everyone's attention to biochemistry and the chemical basis of metabolism and disease. Organic chemistry has long been an "acid test" of premedical education, and a peek at current (2018) premedical curricula confirms that regular, organic, and bio- chemistry dominate the requirements, with mathematics and physics not ignored but rather trivialized.

There is an ingrained legacy of this 150 year old attitude – the assumption that every dynamic in the body is a chemical reaction, and that clinical and laboratory diagnosis are always looking for the chemical basis of what is wrong. A simple example for wounds concerns nutrition. Those who know nothing about wounds always think that if you stuff a patient with burgers and fries then the wound will heal. It is an erroneous and silly concept, but it has an historical basis. Twentieth century physiology was informed largely by chemistry, where simple chemical reactions have simple reaction kinetics. Consider a basic chemical equation such as [A] + [B] ⇆ [C]. In a test tube, you can pour more substrate on the left side of the equation, and more product comes out on the right side. Therefore, so the thinking goes, just pour more chicken fried steak and coconut cream pie into your patient, and all things metabolic will speed up, the wound will spew collagen, and your wounds will magically heal. The problem of course is that is not how nutrition, wounds, or any other physiological system work. These systems are highly regulated control systems mediated by cells, organelles, and enzymes, and substrate utilization does not follow simple linear kinetics.

That is the legacy of 19th and 20th century science on the mentality of physiology, a bias towards basic chemical and biochemical dynamics (e.g. Michaelis-Menten enzyme-substrate conversion), and the linear characterization of how any 2 chemicals react. For example, the Krebs and TCA cycles were mapped by looking at the kinetics of dual-species conversions, such as citrate-aconitate or fumarate-malate. However, the composite behavior of these cycles could only be reduced to those big highly interconnected wall charts that overwhelmed you in medical school. Trying to understand, model, or predict the integrated operations or state spaces of those complex systems was beyond the analytical or computational means of those times. Instead, biological research, doctrine, and dogma became anchored in the dependent-versus-independent method of experimental biology based on simple linear interactions. This mentality went from test tube to the clinic, where RCT's, randomized controlled trials, became the gold standard of exploring the effects of a single agent or intervention on the net behavior of a system. This approach to science has substantial limitations, because it can never elucidate the comprehensive integrated behavior of complex n-element systems. Instead, complex, non-linear, and n-body systems were deprecated as "intractable", and consequently not worthy of study. Within the halls of biomedical academia, there was, and largely still is, little room for understanding or teaching biomathematics and physics based overall systems biology.

Much of what we now consider systems dynamics was simply rolled into the overarching idea of "homeostasis" as defined by physiologists ***Claude Bernard*** (1813-1878) and ***Walter Bradford Cannon*** (1871-1945). This concept is that organisms or systems maintain their "internal milieu" in a stable desirable state, achieved through regulatory mechanisms, dynamic equilibria, and steady states between components of the system. We recognize easily that this implies "control", that "desirable states" are system references, and that regulatory mechanisms are the control blocks and signals in a control loop. On that cutting edge of 19th – 20th century biology, "equilibrium", a chemical reaction concept, was important to the idea of homeostasis. The reality though is that non-linearity and control, creating stable but non-equilibrated chaotic attractors, are the core dynamics of all healthy complex biological systems. The confusion is understandable, because back then chemical equilibrium was an au courant concept of the times, and non-linear dynamics was a fantasy that few envisioned. However, even then, there was at least one biological closed loop feedback system that was known and taught to medial students - the hypothalamic-pituitary-endocrine system. It is often portrayed as an interesting oddity that a feedback system even exists, not true at all, but it is a convenient starting place to illustrate control and non-linearity in biological systems.

The Endocrine Control System. The endocrine control system has been abstracted here to a uniform loop that actually regulates several different organs and system references. Whether dealing with thyroid, adrenal, gonads, or growth, the system reference is some manifestation or measure of "normal metabolism". The feedback in the loop is the level of end-organ hormones (thyroid, adrenocorticoid, gonadal, anabolic), either those hormones themselves or some metabolite of them or some further downstream metabolite resulting from their biological effects. The system comparator is the hypothalamus, which through some black-box mechanism monitors the balance between the reference value and the actual concentration of hormone or metabolites. If there is a variance, then the hypothalamus issues an error signal in the form of the releasing hormones (trh, crh, gnrh, ghrh). This signal drives a controller, the pituitary, which amplifies the signal and has the "power" to drive the system load. It drives the load via a control signal in the form of the stimulating hormones (tsh, acth, fsh-lh, gh). The load itself is the peripheral endocrine organs and other tissues – thyroid, adrenal cortex, gonads, and liver & mesenchyme. The system output is the set of peripheral endocrine hormones that regulate whole body metabolism and related functions (thyroid hormone, cortisol, progestins, etc.). They or their effects are then transduced and fed back to the system comparator.

In human engineered systems like nuts-and-bolts machines and electronic circuits, systems can be designed with a few well-defined elements. In complex biological systems, there can be dozens or hundreds of elements, so diagrams such as this are abstractions that roll many items together into each of the control blocks. In abstracting the system, in reducing the many to the few, there can be options deciding how to parse or assign elements to the simplified blocks. For example, this loop could be drawn with pituitary and even the end-organs being amplifiers on the hypothalamus output, then some manifestation of general cell and substrate metabolism as driven by the endocrine hormones could be listed as load and output. The Wound is another regulated system with many elements, so to model it, abstractions and simplifications are necessary, but the roles of the major biological components of wound healing are clear enough that a standardized wound control loop can easily be defined.

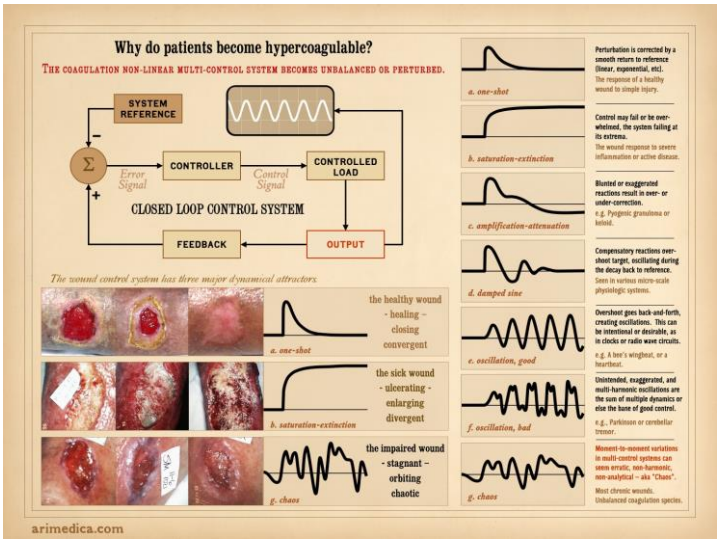
The Wound Control System. Like nearly every other system in physiology, the wound is a regulated controlled "machine". Like all other systems, the proliferative module of normal post-inflammatory wound healing must be regulated if it is to remain within its operating range. It must be regulated so it knows when to turn on, how much output to create, and when to cease. This regulation is a non-linear process based on a closed feedback loop having all elements of any well-controlled machine. The many anatomical constituents and physiological events of the wound module all correlate with or map to basic elements of the wound control system. Presented here is a basic description the Wound control loop.

A ***wound*** results from some type of ***injury***, provoking the integrated response that has the afferent injury response component ***inflammation*** which in turn leads into the efferent restorative process ***wound healing***. Dynamically, the response to injury is a closed loop feedback regulated control system. The **Wound Main Control Loop** has the elements of any control system. The **system reference** is normal tissue which is closed (epithelialized) and free of disease, injury, and inflammation. How the body recognizes this condition, i.e. what physiological or anatomical properties constitute closure are biologically important, but with regard to dynamics of the loop per se, they are anonymous abstractions. Likewise, each control element is a proverbial "black box" having numerous internal biological parameters which somehow transform an input into an output, but looking to upstream and downstream neighbors as a single element. System reference is continuously compared to actual state of the wound, and any variance of the wound away from "closed" generates an error signal. The system comparator and **error detector** are the recognizers-sensors-transducers of injury, mainly leukocytes, platelets, and related chemicals. Their activities and consequences are to initiate and mediate acute inflammation, the result of which, their output, is inflammation itself. Inflammation, with its chemical and cellular effects, is the **error signal**, the way that the system comparator tells the system controller what to do. The **system controller** is the macrophage. The error signal boosts macrophages and turns them on to do their wound functions, both afferent (M1 inflammatory macrophage) and efferent (M2 repair macrophage). The efferent function is to issue pro-proliferative growth factors, the **control signal** which will actuate and drive the system load. The system **controlled load** is the set of cells which do the actual work of building tissue and thereby correcting "open wound" conditions. Repair cells are angiocytes and fibroblasts which restore the mesenchymal stroma, and the epithelial cells which close and sequester the mesenchyme. These cells are the load. What they create is the **system output**, mainly ground substance, vessels, connective matrix, contraction, and epithelialization, those things that are explicitly the new or adjusted tissue which reduces "open wound" and corrects the system error. Finally, the new state of the system must be reported back to the system comparator. The **feedback** is the residual open wound, with various "black box" attributes of "openness" being transduced by the error detectors. Note the circle leading into the feedback block. The system output has the effect of diminishing the state of "open", so that effect on the "open wound" block is a negation, an inhibitory or inverting input, represented by the circle.

As with the general control system diagram, there is no start or stop, no on-off switch. As long as there is "open wound", the control loop runs, always striving to restore the system to its reference value of closed. If the reference value is reached, then the output of the main summation-comparator node is zero, and there is no force driving the loop. For any controlled system, as soon as there is any intrinsic decay or drift in the state of the system, or else any perturbation due to extrinsic stresses, then the compared value is no longer zero, and an error signal is generated and the loop is driven. For the endocrine control loop, the reference (hormone or metabolism level) is always some positive value, so it is intrinsic decay or drift which is the variance which drives the system, and the system is continuously active and driven from birth until death. For the wound, extrinsic perturbation is what drives the system, in the form of injury. When the wound settles back to "closed", there is no error, and the loop remains quiet. Injury instantaneously creates a condition of "open wound" which enters the loop at the feedback block, immediately generating an inflammation error signal, and the loop then runs autonomously until the wound is closed. Knowing when to start and stop is not a matter of knowledge or intelligence within the system, it is just a matter of a well-tuned control loop operating as designed.

With respect to coagulation, the principles of control are the same. Coagulation works in a time frame that is finer or more narrow than endocrine-metabolic functions and wound healing, but the principles of control are the same. One simple way to model this system is that ***system reference*** is "no open vessel" or "no thrombogenic surface". The ***error signal*** is platelet or tissue thromboplastins and related. The ***controller*** is the plasma activation cascade (factors V, VII, VIII, IX, X, XI, XII, and II-prothrombin), and the ***controlled load*** is fibrinogen-fibrin and the clot it makes. ***Output*** is lack of bleeding and sequestration or masking of the thrombogenic surfaces, and the ***feedback*** is the state or degree of thrombogenic material exposed. Recall though that this is a complex multicontrol system. That means that, for example, prothrombin and thrombin must have blood levels that are properly tuned to spring into action as controller and load to make a clot "on a moment's notice". Regulation of each their concentrations are themselves closed loop control processes. Degradation of thrombus once it has occurred is also a closed loop control process, with plasmin and other lytic factors rising in response to fibrin conversion, then subsiding back to baseline when thrombus is lysed. When a system this complex

and interconnected gets unbalanced by intrinsic variances or gets perturbed by extrinsic activation, it is easy to see how it could shift to a different reference or set point or trigger point, or become dampened in response or overly excited. It could drift or fail or relevel itself going low causing a clinical state of hypocoagulability and excessive bleeding, or it could drift or fail or relevel itself going high causing hypercoagulability and errant intravascular thrombosis. It also means that responses to deliberate perturbation, such as treatment with anticoagulants or prothrombotic drugs could have unintended or unexpected responses, possibly attenuated or amplified, erratic or contradictory.



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Dynamic Behaviors of Complex and Disturbed Systems

Someone might have hypercoagulable gene R506Q Leiden, but he will be hypercoagulable only at times, and other times not. This is because, as a multi-control system, coagulation exhibits dynamical behaviors that can seem erratic at times or dwell in the wrong place.

Non-linear and control systems can have a variety of free-running behaviors or dynamical responses to perturbation. These responses or attractors can readily be recognized in "slow" systems such as a wound, but they can also be measured and recognized in fast and intermediate systems such as endocrine and blood physiology (with the support of the chemistry lab). Understanding the generic range of responses helps predict or understand variances in disease activity, clinical status, and responses to treatment. This is as true for coagulation as it is for endocrinopathy and altered wounds.

A frequent example of problematic control related to coagulation is the effort to regulate warfarin doses in patients with thrombophilic and hypercoagulable disorders. Recall that warfarin, as important and life-saving as it is, is a difficult drug to use. It has a low therapeutic index (toxic dose ÷ effective dose). In that sense it is like many other valuable drugs that can be lethal or life saving depending on dose, e.g. dicoumarol derivatives, digitalis glycosides, narcotic opioids and barbiturates, anti-neoplastic vinca alkaloids, hepatotoxic acetaminophen and ulcerogenic aspirin, and countless others. Some of these drugs, such as opioids, need caution but they are easy to use because their pharmacokinetics are simple and short. Assuming you have a normal liver, an effective pain-relieving opioid dose can be re-dosed in 3 or 4 hours. Warfarin, like digoxin, phenytoin, and others has more complex pharmacokinetics. These are similar in that they have long half lives and very low toxic thresholds. For warfarin, (1) its metabolic clearance is slow, and (2) its therapeutic effect is actuated through intermediaries, its effect on vitamin K and in turn on liver production of plasma factors. The result is propagation delays in its effect, and its therapeutic intent can be upset by factors that affect the intermediaries, thus for instance why dietary elements can so easily perturb warfarin balance. This means that the drug has two problematic dynamics: (1) its half life in serum is long, approximately 24-36 hours; (2) its time constant of biological effect is about 36-48 hours (time constant is a physical property of "first order" dynamical systems that have exponential responses to step changes, "time constant" being the interval required to get to 1/e of the final asymptotic value, roughly 63% changed, 37% left to go). This means that the PT-inr you order to check therapeutic status reflects the dose of warfarin you gave 2 days ago. The cumulative effect is that warfarin dosing is perpetually out of sync with normal diurnal physiological processes, normal dosing schedules and patient care pragmatics, the vicissitudes of diet, other mediations, and other metabolic factors, and that a safe and effective daily dosing schedule must be worked out individually for each patient.

Consider a prototypical use of warfarin, to prevent mural thrombus in a patient with atrial fibrillation. Warfarin is never assured to be easy to regulate, but it is most likely that this patient has otherwise normal blood, plasma, and clotting profile. For most such patients, a stable dose of warfarin is usually found soon enough, a stable dose that holds prothrombin time PT-inr around 2.0-2.5 without too much drift, and which will be an effective and non-toxic dose for that patient for many months or years to come. Now, compare that to the typical hypercoagulable patient. These patients frequently give the following history, or you will experience it yourself if you try to prescribe the drug. The story is that warfarin was started but had to be stopped. Either it was too erratic to use, never finding a stable dose, PT often drifting far too high, or the patient was resistant to the drug, never showing an effect or treatment abandoned when daily dose approached 20 or 30 mg. Infrequently, the patient will have warfarin skin necrosis or other thrombotic event, sometimes fatal while the medication is being initiated. The reason for these erratic and problematic situations is that in a patient with a well tuned coagulation system, a perturbation such as starting warfarin will be matched by orderly and asymptotic responses that re-regulate the system to a new reference and then hold that new line with relative ease and stability. In systems already untuned or unbalanced, even if subtle and not overtly decompensated, systems in which controllers and regulators are altered or improper, the response to another perturbation will become exaggerated or chaotic. To understand why, first consider the general ways in which feedback regulated closed loop control systems respond to perturbations.

Illustrated is a generic control loop. Some parameter, in this case the system output, is being monitored so that timewise responses to stress can be seen. To appreciate them, remember the basic purpose of control. Systems must be at a certain value or operating range to function as intended. However, systems might not stay put. There can be decay or drift of intrinsic parameters, or perturbation by extrinsic forces. A control system monitors itself. If it senses variances from reference, it tries to correct them and restore the system to reference value. The system tries to counteract changes, pulling back in the opposite direction of the unwanted change. If the system drifts low, the control loop pulls up. If the system is pushed high, the control loop pulls down. The control loop is always trying to reverse the direction of unwanted variances, trying to keep the system as close as possible to the reference or target level. Ideally, corrections are made as quickly and smoothly as possible. However, there can be errors or instabilities in the correction itself, leading to over correction, under correction, or a variety of dynamical behaviors. Whether or not the system behaves as needed depends on the quality and tuning of the circuit. In engineered systems, man made machines can deliberately be designed and tuned to have specific types of responses. In natural and biological systems, the quality and tuning of the responses represent evolutionary adaptations based on principles of thermodynamics and non-linear dynamics. On the right side of the panel is a sampler of seven

generic responses of controlled systems to inputs or stress, mostly impulse functions which are instantaneous perturbations that the control loop must react to. The discussion of each gives physiological examples, many of which are derived from wound physiology. However, if you think about the circumstances of hypercoagulable blood failure, and especially about hypocoagulable blood failure which most doctors are quite familiar with, you can draw suitable parallels.

One-shot. Perturbation is corrected by a smooth return to reference (linear, exponential, etc). *The response of a healthy wound to simple injury.* An incidental perturbation or trigger suddenly knocks the system to a new value. The change from baseline is corrected by a smooth return to reference or baseline - convergence. The dynamics or mathematical nature of the return can vary based on the nature of the system. The decay could be at a constant rate (zero-order, linear), or at a rate proportional to its current value (first order, exponential), or with some other dynamic. First order decay occurs in systems in which rate of change of the measured element is proportional to its current concentration, the mathematical solution of which is exponential rise or fall. It is generally the most common dynamic in natural systems (chemical, electrical, mechanical, physiological, etc). This will appear as the typical curved asymptotic graph illustrated. This is the ideal response to perturbation, the way engineers would want to make most machines behave. Common examples from biology include the serum concentration of a drug after a one-shot injection, the relaxation of tension in a stretched scar, and the response of a healthy wound to simple injury. Normal wound healing, its aggregate closure as well as many individual components, and especially the overall dynamics of the Wound Main Control Loop, will exhibit this response to the initial injury, assuming that the system is healthy and that the injury was a one-time instantaneous event. *For coagulation, a likely analogy would be the restoration of serum fibrinogen to normal level after some has been consumed for a simple uncomplicated minor trauma.*

Saturation-extinction. Control may fail or be over-whelmed, the system failing at its extrema. *The wound response to severe inflammation or active disease.* This may happen when: (1) the intensity of the perturbation drives the healthy system out of bounds of its operating range (the extrinsic disturbing force is greater than the strength of the system to respond); (2) the system is intrinsically inadequate or has become faulty so that it cannot respond as designed to forces which would otherwise be within the response range. The effect is that the system fails at its extrema, reaching its maximum physical capacity to respond, or exceeding its operating range and design limits (dynamical divergence). It could go into saturation, failing at the upper or loaded end of the range, or it could go into extinction, becoming zero. Either way the system was meant to be operating somewhere in between, and it has now been forced up or down out of the operating range. Since the system is no longer in its operating range, it can no longer function and respond to the altered state, and thus it cannot correct itself. The system will then remain in its saturated or extinguished state until the perturbation is relieved (or the system machinery is repaired). As a biological example, consider a patient with congestive heart failure, cardiomyopathy, and coronary artery disease who is currently compensated and free of acute symptoms. Suddenly the patient goes into florid failure due to a hypertensive crisis or the onset of pneumonia or peritonitis. Sudden changes in afterload or cardiac work and preload will change many parameters such as myocyte fiber length, ventricular diameter, ventricular dp/dt, etc., i.e. those physiological parameters that must be properly "tuned" if the myocardium is to remain in its proper operating range and be an effective pump. Oxygen delivery and energy utilization are important for proper myocardial function, but those too are impaired by coronary artery disease. See what is happening? The acute extrinsic stressors result in decompensation of fiber length and ventricular diameter which push the pump out of its operating range. The coronary artery disease is loss of an intrinsic component, loss of a "degree of freedom" in the system's innate ability to react and compensate. As the failure begins, conditions which provoke failure get even worse (a non-linear amplification), and the decompensation progresses until there is no chance of the system ever pulling itself back into proper operating range. The various parameters are out of bounds, either high or low, saturated or extinguished. If the pump is physically damaged e.g. by an infarct, then corrections may be impossible. However, if the machine stays inherently undamaged, then interventions to restore the proper operating range will allow the system to come down from its saturated state and start again to actively control and properly regulate. Treating hypertension, volume overload, systemic metabolic load, or coronary artery occlusion are the types of interventions which can pull the system back into operating bounds. As a wound example, saturation is the response to severe inflammation or active disease. Under conditions of active disease and ulceration, the repair process cannot prevail over the destructive events. The repair process and control loop become saturated – on full time "overdrive". What is happening is that the error detector sees a widening discrepancy between normal and actual state, so the system gets driven to maximum capacity. However, the control loop is "blocked" or "open circuit" at the system output stage, because output is being suppressed or destroyed by the active injury and inflammation. No output means no correction of the system state. Therefore "open wound" feedback does not diminish (in fact it gets worse due to disease and inflammation). The system error persists and the front part of the control loop remains maximally driven and operating at its peak physical capacity, i.e. saturated. So, the system is saturated, but nothing productive happens. Alleviating the active disease and injury will allow the control loop to reenter its operating range. *For coagulation, a likely analogy would be DIC, disseminated intravascular coagulation. Whatever triggers it, it incites diffuse activation of plasma and platelet thrombotic pathways and also rapid consumption of promoting and inhibiting species. Thrombosis gets locked into an attractor in which clotting rapidly propagates and begets more clotting (system is driven out of its operating range), and the capacity of the liver and bone marrow to replenish depleted species is overwhelmed.*

Amplification-attenuation. Blunted or exaggerated reactions result in over- or under-correction. *e.g. Wound – pyogenic granuloma or keloid.* The response of the system to perturbation might be qualitatively correct but quantitatively incorrect – too much or too little. If the response is amplified or exaggerated, then there will be an over-correction. If the response is blunted or attenuated, then there will be an under-correction. If the loop continues operating, there will be subsequent opportunities for the system to correct itself, but if the imbalance is system wide or consistent, then it will repetitively miss the mark. Biological wound examples that seem to fit this dynamic are pyogenic granulomas and keloids, in which the wound healing process is amplified, exaggerated, and overshoots the intended target, making too much wound healing and too much new tissue. *For coagulation, a likely analogy would be hemophilia, with deficiencies of factor XIII or IX. Patients with mild forms can have up to half of normal levels of these factors. In the stress or perturbation of injury or bleeding, thrombosis will occur, but more slowly and inadequately. Bleeding therefore will continue longer than normal with ecchymosis or hemarthrosis or similar, but the bleeding can nonetheless stop. The integrated coagulation response is attenuated, qualitatively correct but never rising to full effect.*

Damped sine. Compensatory reactions over-shoot target, oscillating during the decay back to reference. *Seen in various micro-scale physiologic systems.* When a controller initiates a correction (implemented by the load), it will have a force or rate changing the system in the desired direction. If sensing, feedback, and actuation were instantaneous, and if the response is well tuned, the correction and return to baseline would settle smoothly on the correct value, a one-shot response. However, in real systems, response times may not be instant. Sensing, feedback, and actuation

of corrections need time to propagate. Delays between an event and sensing, or between sensing and response, mean that by the time a response starts or peaks, the state that provoked it may have already changed. Out of phase with the stimulus, the response can overshoot or undershoot the target, even start oscillating. For example, if a response is too fast or strong, it can overshoot the system reference it is trying to get to. Having gone too far, the error is now in the opposite direction, and the controller must reverse to bring the system back the other way. However, timing delays mean the controller learns of the overshoot only after it has started, and corrections it makes need additional time to kick in. The system thus keeps moving in the wrong direction awhile before it feels the pull and starts moving back the other way. Now going in the opposite direction, the system tries again to get to baseline, but time delays being an inherent property of the system, it overshoots in the other direction, and the pattern repeats. This sets up a cyclical back-and-forth dynamic around the reference value. With each cycle though the control gets better as the system "loses steam", steadily giving up some energy, sooner or later coming to rest at the target value. Instead of a simple one-shot exponential return to baseline after perturbation, the effect is that the system "rings", a transient oscillation as it decays back to reference (the peak-to-peak envelope will be the expected exponential decay). This oscillation modulating the decay is a damped sine wave. It is the brief waveform you see on the screen when you turn power off to a CRT display (television, monitor, oscilloscope). It is the transient wiggle of a spring stretched and released, the slowing of a pendulum due to friction. Damped sine waves are seen in biological systems, typically in micro-scale studies of neurological, cellular, and chemical physiologies. If you work with spine injured patients and have a chance to observe the reflex muscle spasms that occur briefly in response to stimulation, they are a perfect clinical example of a damped sine wave as the spasm triggers then decays.

Oscillation (good). Overshoot goes back-and-forth, creating sustained oscillations. This can be intentional or desirable, as in clocks or radio wave circuits. *e.g. A bee's wingbeat, or a heartbeat.* Not all oscillations are transient or damped, and not all are bad. Free running oscillation is in fact the goal and healthy productive state of many systems. Principles of feedback, reactive correction, overshoot, and timing and delay can all be engineered and tuned such that the back-and-forth over-correction under-correction becomes deliberately sustained. All systems have energy losses which will damp an oscillation, so for it to be maintained, new energy must be repetitively restored to the system, and when it is, oscillation can be sustained indefinitely. These principles allow us to build clocks and radio wave circuits and engines and all kinds of things. For example, the wound spring inside a wristwatch or the weights in grandfather clock provide the energy needed to overcome friction losses and keep the timing pendulum moving. Biological examples of autonomous periodic, i.e. oscillatory systems include a bee's wingbeat and a heartbeat. Overt fixed rate oscillations are not evident in wounds. *For coagulation, it is hard to conceive of harmonic variations of any clotting factor or its properties (concentration, zymogen conversion rate, etc.) having clinical relevance, but since there are test tube chemical reactions that are famously oscillatory, it would be an interesting physiological observation to see if any of the coagulation species vary that way.*

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.* In mathematics, all periodic or harmonic (oscillatory) functions can be represented by a polynomial of sines and cosines (a Fourier series). Engineers use this principle to combine different frequencies to create any arbitrary waveform. The same principle works in reverse to get information out of combined waveforms, such as decoding a particular channel from all of the information that comes through a single television cable. So, multi-harmonic oscillation can be a good thing, but when it shows up unintentionally, or it is exaggerated, or it is the result of unintended subsidiary circuits and feedback loops in complex systems, then it is unwelcome and can be the bane of good control. All clinicians are familiar with the concept from looking at ECGs that are blurred by 60 Hz crosstalk from nearby electrical devices and wall power. As an impairment of control in biological systems, Parkinson's disease and cerebellar and other tremors are examples of inadequate or delayed control resulting in problematic single or multi harmonic oscillation.

Chaos. Moment-to-moment variations in multi-control systems can seem erratic, non-harmonic, non-analytical – aka "Chaos". *Most chronic wounds. Unbalanced coagulation species.* When systems, circuits, and machines seem erratic and unstable, the problem could be unwanted oscillation, or it could be noise and random variability. However, variability in multi-control systems is usually due to something else – chaos. If you measure any complex natural multicontrol system carefully enough, especially biological systems, you will find that orderly repetitive functions like breathing are not strictly fixed rate sinusoidal oscillations. Other complex systems can look overtly erratic. If you analyze them mathematically, you will find that they are non-harmonic and non-analytical (not reducible to conventional functions of algebra and calculus), but neither are they gaussian or random. Even though they seem erratic, these systems are obeying precise physical rules and principles. This is chaos, the behavior of complex non-linear systems. "Chaos" is an unfortunate term because in physics and math it means something different than it means in the vernacular vocabulary. Chaotic systems behave in seemingly complex ways that cannot be described by simple harmonics or differential equations or attributed to randomness and noise. Chaotic systems are highly deterministic and rule-driven, and highly organized and structured. The trick is that from the seeming erratic state of the system, you need to know how to look for that structure and graph it if the face value data stream is to make any sense. Most chronic wounds are chaotic, their dynamics revealed as the wounds are observed over time. The origins of chaos in the wound will not be discussed in detail here, although its relevance to clinical wound care is described next. *For coagulation, chaos arising from the complex non-linear multicontrol thrombosis system. will be described on the next two panels.*

The Wound and applied non-linear dynamics. Engineers making electrical and mechanical devices will deal with all the responses and instabilities described here. Examples have been given of these behaviors in controlled biological systems (and remember, biological systems are all controlled). However, every system has its own physical and dynamical realities, and thus its own characteristic ways of failing or misbehaving. For wounds, not all of the above responses apply. Harmonic oscillations are not relevant. We often see amplification and attenuation in response to various applied therapies, but that does not reflect the intrinsic dynamics of a given wound. The core dynamical behaviors and misbehaviors that are a part of everyday wound physiology, pathology, and clinical management are three: one-shot, saturation-extinction, and chaos. To appreciate this, it is crucial to understand that non-linear multi-control chaotic systems tend to dwell in basins of relatively stability. When a wound or any system enters one of these ***attractors***, it has entered a state of dynamical and thermodynamical cohesion and sustentation from which it can be hard to break out. The wound control system has three major dynamical attractors:

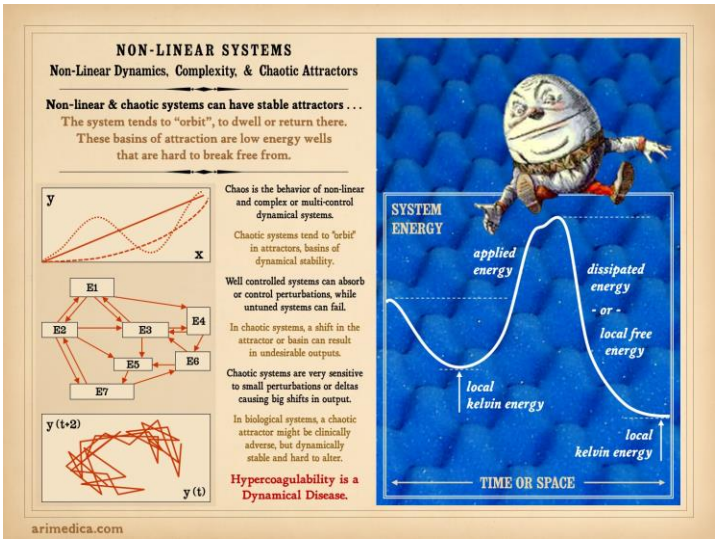
Healthy wound. The healthy wound is ***healing and closing***. Its kinetics are a ***one-shot***. It is in a dynamical state of ***convergence*** on the system reference of "healed". In the healthy wound, injury is an "impulse function" that suddenly jumps the wound from non-existent into an elevated state. From there, the control system brings it back down to normal (healed) along a simple trajectory of "decay", ideally a smooth return from open and disrupted back to closed and reorganized.

Sick wound. The sick wound is ***ulcerating and enlarging***. Its kinetics are ***saturation- extinction***. It is in a dynamical state of ***divergence*** away from the system reference. In the sick wound, primary disease and injury are at work, causing active necrosis and ulceration by thrombo-infarctive and inflammatory-lytic mechanisms. The control loop is either overwhelmed (saturated) by the strength of the perturbation, or it is suppressed (extinguished) by one or another inhibitory means. The wound is divergent, becoming more of a wound rather than less. Clinically, this is an undesirable state, but dynamically it is a stable self-sustaining attractor. Bringing the wound back into the operating range of the control loop, where individual components of the control loop are not overwhelmed or suppressed, where the wound healing machinery can then operate to heal the wound, requires deliberate active treatments to abate the disease and injury.

Impaired wound. The impaired wound is ***static or stagnant***. Its kinetics are ***orbits***. It is in a dynamical state of ***chaos*** with seeming erratic values that neither converge nor diverge. The impaired wound is not actively sick from acute injury but nonetheless it will not heal. Its clinical appearance is perpetually back and forth in size and status, but never overtly flaring out of control and getting worse nor settling down and making meaningful improvements. Exam-to-exam, for many months, there is no net change in the wound. It does not necessarily get worse when low levels of primary disease are active, and it does not get any better despite of a wide range of diligent treatments. The system "orbits" on this attractor. Orbits are the behavior of chaotic systems which neither converge nor diverge. They hop from value to value eventually returning to a prior value and running through the cycle again.

To reiterate, these are the real world non-linear behaviors of natural complex multi-element multi-control systems. The wound is a biological system with cells and chemicals, but the dynamical behaviors in a wound are common to all complex systems. Crucial to understanding these chaotic systems is that they can dwell in basins of stability, attractors which can be hard to break out of. Of the three wound attractors, one is clinically desirable, and the other two are not, but all three are dynamically and thermodynamically stable and self-sustaining. Clinically, this means that it can be difficult or seemingly impossible to get the impaired wound to behave otherwise.

A similarly detailed explanation of dynamical attractors for the coagulation system is not presented here, but the generalities of it can be inferred by analogy to the wound system. Just like the wound and most other biological systems, coagulation and thrombosis is a non-linear multicontrol system that can stay stable and on reference when healthy, but which has risk of saturating into a hyperthrombotic state, extinguishing into a hypocoagulable state, or orbiting in an abnormal range where clinical status is variable, morbid, and not necessarily easy to correct. This is explained further on the next two panels.



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Non-Linear Systems and Chaos

Complex non-linear systems characteristically can have erratic dynamics. Responses are not analytically related to inputs, small changes can have large responses or vice versa, and systems will dwell in basins of stability. This makes disease and treatment unpredictable.

This panel explains why non-linear systems can dwell and be stable in certain "basins" or "attractors", and they can be hard to break from those stable states. The problem is that stable dynamical states do not necessarily imply clinical desirability. When problem wounds misbehave despite treatment, or refractory coagulopathies seem to randomly enter a phase of misbehaving when they were not before, it is because they are locked in dynamically stable basins.

Dynamical chaos arises in multicontrol complex systems. Those two adjectives each have important implications. Inherent in ***multicontrol*** are concepts of feedback regulation and non-linearity. ***Complexity***, which also arises from non-linearity, is an inherent property of any system with three or more mutually interacting agents, known as the 3-body or N-body problem. ***Non-linearity*** means that a system is self dependent. Its state in the next iteration or timeslice is dependent on its current state. That means that its current value must feed back into itself to regulate what comes next. The term "non-linear" means different things depending on context. It can mean just a straight line. In the ***upper of the three small panes*** on the left, one of the functions is a simple y=x straight line, linear. The other two curved lines are not straight, but they too are linear in the sense that they are not non-linear. What makes them linear in this context is that they are proper functions, y=f(x). The output or dependent variable on the y-axis maps one-to-one to the input values of the independent x-axis. Non-linear systems, in the dynamical sense, cannot be graphed this way. Output y is not a function of input x. Instead, the state of the system x is a function of itself as it moves through time, $x_{t+1} \leftarrow f(x_t)$, the arrow indicating that the two states are not equal, instead one maps onto the other. Feedback and the ability of the system to regulate itself are inherent in these dynamics. All closed loop feedback regulated systems are thus non-linear in the dynamical sense. Non-linearity can lead to some very interesting dynamics.

To illustrate the difference between linear and non-linear systems, consider two different kinds of pumps. One is a simple man-made piston pump. The other is the heart. In both, the output or flow (p) is the product of the stroke rate (r) times the stroke volume (v), $p = vr$. For the simple pump, the machine is made so that stroke volume (v) and stroke rate (r) can each be adjusted by the operator independently of each other. Each is an independent variable of the system, neither contingent on the other. Thus, $p = f(v)$ and $p = f(r)$, but v & r have no dependencies. The total flow or output varies as v and r vary. If v and r vary concurrently, you can still directly calculate variations in flow by prorating the contributions of each independent change (even if the parameters vary continuously, which is the purpose of partial differential equations: $dp = v\partial r + r\partial v$). This is a simple analytical non-linear system. Its output can be functionally graphed. Simple. Non-linear. For the heart, cardiac output also equals stroke

volume times heart rate, p = vr, just like the steam pump. But, there is a crucial difference between the two pumps. In the heart, as in the steam pump, p = f(v) and p = f(r), but also v = f(r). Consider a basic point of physiology: as heart rate increases, stroke volume can diminish because diastolic filling time is impaired, i.e. volume and rate are contingent. Another point: as stroke volume increases (as during exercise, due to increased venous return), ventricular stretching drives a higher heart rate, i.e. rate and volume are contingent. Each is a function of the other. There are three "bodies", three independent variables, three mutual sets of functional dependencies.

For ordinary equations y = f(x) such y=2x+3 or $y=x^2$ or $y=e^x\sin(x)$, there is a precise correspondence between input and output values. Enter any arbitrary x, and you know exactly what y is. For 3-body problems, there is no general solution, no function to perfectly calculate the value of one of the variables versus time or the other variables. All you can say is that y = f(x,z), x = f(z,y), and z = f(y,x). The problem is that y is partly a function of x, but x is also changed by z which itself has been altered by both of the others. If you want to study or model the system numerically, you cannot do so by ordinary equations that plot y versus x. Non-linear and n-body problems are "solved", mapped in time, by ***iteration***. The method of iteration is predicated on the idea that y = f(x,z) is valid using the current values of y and z for infinitesimally small intervals, and if you update all three equations simultaneously with current values, the new values should be minutely close to reality, and then you use the new values and solve the system again, a new iteration. The thinner the timeslices, the more calculations you do, then the more accurate the model is in describing real world dynamics of the system. Of course, numerical modeling is just our way of studying what nature is doing automatically and continuously.

Note that each time you iterate, you are plugging the system values back into the system operations. This is the very definition of feedback, which ipso facto makes this a non-linear system. In nature, such systems generally have ways to sense and monitor the feedback and compare the system state to a reference, thereby not allowing any parameter to get too far out of bounds. Thus, if the next value of z is about to break bounds of its physiological limits, its own system controller will shove it back the other way. The value of y, which is contingent on z but otherwise is in a "happy place" of its own operational range, now has a sudden perturbation as z is snapped back. Maybe y stays in its proper range, but if it gets rocked too far, then its controller must respond to reel it back in. The changes in z and y in turn affect x which itself feeds back to affect the others. The endless push-pull influences might make any of the parameters seem to buffet back and forth erratically, but the parameters can also find mutually stabilizing values that lock each other into a sedate "quiet zone". This is chaos. Each mutual dependency is based on strict physical or mathematical rules, but throw them all together, and strange or "chaotic" behaviors appear. In both nature and computer simulations, whether in a quiet attractor or on a wild looking trace, this is chaos, the behavior of n-body and non-linear systems. If you try to analyze the datastream, it will not fit any type of ordinary mathematical function. If the trace varies back and forth around some mean or baseline, you might think that there are sinusoidal waveforms in there, but an inverse Fourier transform will show no dominant harmonic. If the trace looks erratic and structureless, you might assume it is random, but a Gaussian distribution will be flat or non-modal. Chaos, being based on deterministic processes, is actually quite structured, if you know how to find it. To the "naked eye" though, chaotic non-linear systems can indeed seem erratic and incomprehensible.

Even the simplest of non-linear systems can show chaotic dynamics when iterated, even systems of just one variable. The more elements, the bigger the "n" in n-body, the more complex the system can become. This is patently true in natural and physiological systems where each element in a control loop is a black box with its own internal controls, where there are subsystems and embedded loops which each have their own feedbacks, dependencies, and regulators. For example, in the wound, the thrombosis-inflammation loop exhibits control. The thrombosis, inflammation, and repair one-shots all have control. Even the way in which an angiocyte migrates then reassembles in response to a gradient field of VEGF is a strictly reference-driven controlled process. All of these events have "hooks" into the other control loops, acting as extrinsic promoters or inhibitors. This matrix of interconnected control loops is "multi-control". When a well behaved simple system should be acting like a one-shot, but various forces and perturbations keep elevating or rocking the system, then chaotic dynamics should ensue. With complex multi-control in natural systems, chaotic dynamics are largely assured. The ***middle of the three panes*** on the left diagrams interconnected control systems. We have all seen diagrams like this, where a researcher or author studies a highly interconnected system and draws all of the arrows between blocks. In conventional 19th and 20th century physiology studies, such drawings were often ignored or deprecated as interesting but not really capable of study. The bias was toward linear science where "everything" is held stable while just one dependent variable y is measured while independent variable x is varied. Interconnect diagrams as shown had no means of dynamical modeling until computers came along circa 1950, but even then, physiology research remains largely linear, looking at distilled elements of a system but not the system as a whole. However, those interconnect diagrams reflect the reality of nature, and they can be studied and modeled with modern tools, and it is in their interconnected architecture that non-linear chaotic dynamics arise.

"Chaos" in its vernacular sense might sound antithetical to classical physiological concepts of "internal milieu" and "homeostasis", but in complex physiological systems chaos is a cornerstone of healthy physiological function. Multi-control is what keeps physiological systems in bounds. The moment-to-moment variability of a parameter might seem erratic, unpredictable, and non-analytical, but a healthy system will keep that parameter within permissible limits, within a certain "state space" or attractor. You might not know moment-to-moment the next value or trajectory of a variable, but you will know that it stays on its attractor unless it gets sick, or that if it gets off its attractor that is what makes things sick. The ***lower of the three panes*** on the left is typical of the kind of mapping that must be done to see the structure in chaotic data sets, in lieu of a function graph as in the top pane. The method illustrated is an "embedding diagram", in which one variable is plotted against itself, its current value y(t) versus its value some number of iterations hence y(t+#). This of course is most appropriate for non-linear systems that feedback and depend on themselves. The embedding diagram assumes that with feedback and control, the value of the system a short time from now will have a functional cause-and-effect relationship to its value now, based on its deterministic rules and physics. In making such plots, structure and attractors can be revealed. It is these methods, rather than algebraic or harmonic or statistical analysis that reveals the organized complexity of the system. Recall the term "orbits" from the last panel. Orbits are the behavior of chaotic systems which neither converge nor diverge. They hop from value to value eventually returning to a prior values or staying within limits or a bounded state space. They are the middle ground between system divergence and convergence. Physiological systems are not only non-linear and chaotic, but they orbit. In biological systems, absolute convergence or divergence is failure and death. Systems that sustain themselves by letting each of their internal elements respond to each other and to extrinsic perturbations, all the time pushing and pulling to keep physiological parameters within their functional range, they are orbiting, never static, always on the move, but never creeping out of bounds when the system is healthy.

Chaos is the way non-linear systems behave, and there is no other choice, no other way about it for n-body multi-control systems. The more layers of control, the more non-linearity, the more erratic the chaos might get, but that is the way that healthy complex systems behave. Chaos in physiological systems is not only normal, not only healthy, but if it disappears that is bad. A seminal demonstration of this was the work of cardiologist ***Ary Goldberger*** (b1949; e.g., *Goldberger AL. Nonlinear dynamics, fractals and chaos: applications to cardiac electrophysiology. Annals Biomed Eng, 1990, 18:195-198.*) As a complex multi-control non-linear engine, heart parameters should be chaotic. If the beat-to-beat time interval of the heart is finely measured, there is plenty of erratic fine variation, and this can be shown by several mathematical tools to be not just chaotic, but a consequence of control (such as the embedding diagram, left bottom). In sick patients with terminal heart disease, the beat-to-beat chaotic variability disappears shortly before cardiac arrest and death, heart rate instead becoming an exact fixed rate, meaning periodic or harmonic. Harmonic periodicity is a sign that many layers of control have gone off line. The most resilient autonomous pacemaker persists for awhile, but systems all around it have collapsed. "Chaos is good, and well-behaved periodicity is bad" . . . the physics of complex systems may seem a bit counter-intuitive if you have not studied the subject. However, that is the way that healthy complex systems are supposed to behave, all a consequence of multi-control.

It was commented above that endless push-pull influences can make parameters buffet back and forth and look erratic, what you ordinarily think of when you hear "chaotic", but the parameters and system as a whole can also find mutually stabilizing values that lock each other into a sedate "quiet zone". This can be viewed as a localized or relative state of convergence, or else an orbit that has little variation. To understand how chaotic systems can at times settle into quiet zones or attractors while at other times being "pumped up" onto highly erratic orbits, the relevant principles are analogous to thermodynamics. A chaotic non-linear system can tend to dwell in or return to a stable attractor, or some major upheaval can force it onto another attractor. Attractors can be thought of as gravity wells or charge wells, a big planet or a small ion that other objects want to orbit or fall into. Consider for example a planet with a satellite. The satellite has kinetic energy that keeps it in orbit. Alternately, consider an elevator raised to the top of a building, suspended in a given position. It has potential energy, ready to be converted back to kinetic energy as soon as it is allowed to drop. If an object drops, or if its orbit decays, the system is giving up energy, and the system is converging to a state of final stability where no more kinetic motion happens unless new energy is put back into the system. Alternately, energy could be put into the system to elevate the orbit by increased kinetic energy, even to the point of escape velocity which would be divergence between the objects. Between convergence and divergence are orbits of variable period, depending on the energy in the system. These concepts use the literal vocabulary of physics, energy, and gravity, but these terms and concepts apply figuratively as well to the attractors and dynamics of chaotic non-linear systems.

All objects have an obligatory basal energy due to temperature and pressure, Kelvin energy which cannot be converted to anything else without giving up heat. It can be transferred to other objects, but if any of it is lost, then the temperature of the body diminishes. Closely allied to this basal energy is the concept of entropy, the amount of heat gained or lost at a given temperature. Entropy will always increase in the "downhill" transfer of energy, so it reflects conditions of equilibration or convergence. Beyond their Kelvin energy, objects can also have "free energy" (Gibbs energy), "free" because it is readily convertible without changing temperature or entropy. This is kinetic energy and potential energy, as stored in the separation of gravitational or charged objects, or in the elastic deformations of a spring, or in the bonds of an energetic molecule. For the orbiting satellite, free energy is kinetic. If it sheds free energy, its orbit decays. If it gains energy, its orbit is elevated. If an elevator is stuck on the 5th floor, it has a certain amount of free energy stored as gravitational potential energy. If it goes up, more free energy must be put in to elevate it. If it descends, it sheds free energy. Free energy is convertible and reusable.

Consider a satellite in orbit. The height or period of the orbit will depend on how much free energy is in the system. If it is an ideal perfectly conserved system, then it remains at altitude without needing new energy. In the real world though, there are energy losses, such as atmospheric drag from a low orbit, but by adding a little energy back, such as from a periodic rocket thrust, it can remain at nominal average velocity, altitude, and orbital period. A watch or a clock is another example where motion of the pendulum or escapement should oscillate forever as long as raised weights or wound springs can be used to offset energy losses from friction between moving parts. Nature and engineered systems are full of systems where, except to replace internal losses, no other energy is needed to maintain motion or current state. The dynamics have three attractors. **(1)** Allow the system to run freely without replenishing energy losses, and it decays or converges, e.g., the satellite falling from orbit or a stretched spring recoiling fully to static position. **(2)** Add energy sufficient to overcome all counter forces, and the object can elevate and diverge from the system, e.g., a rocket that achieves escape velocity or a spring stretched beyond its elastic limit or yield point and breaks. **(3a)** Periodically add energy to the system just enough to balance energy dissipated internally or transferred to another object, and the system orbits, e.g. the thruster on the satellite. **(3b)** Arbitrarily add or subtract energy from the system to shift it to a new level of free or total energy (and then maintain that new level with periodic balance thrusts), and the system will move to a new orbit, higher or lower, faster or slower.

The implication of "orbit" is the same for a real or abstract dynamical system of any form as it is for a satellite with angular velocity around a center of gravity. They all have the same general types of attractors that allow convergence, divergence, and orbits. In many non-linear chaotic numerical systems, iteration of a parameter will yield numbers which literally repeat themselves every Nth iteration, always returning to the same cyclical values. That is an "orbit" Consider a satellite in physical orbit around the Earth. If it has a small thruster that fires continuously at very low levels to perfectly offset drag, it would stay in a perfect circular orbit. If it just fires once every orbit or few orbits to offset cumulative losses, then altitude will drift down slightly between firings but then pop back up acutely. Say that the boost comes once an orbit, always at the same exact location, so that every cycle or orbit is superposable. To a moon man watching, he would see a repeated sawtooth pattern to the orbit. If you sampled altitude or velocity data every 15 degrees, you would have 24 data points per orbit, and they would follow a pattern that, for every orbit, repeats itself. Now, consider that the boost comes not once every 360° but rather every 390°. The peaks of the sawteeth would have 30° offsets, and the entire pattern would be superposable only after every 12th orbit, but nonetheless, the values would eventually repeat. To the moon man watching, it would trace out a pattern that you could draw with the famous Spirograph® toy (Kenner, Inc. and Hasbro, Inc.), known technically as a guilloché pattern. The density of the guilloché would vary with the proportionality or rationality of the thruster timing with respect to earth circumference, but one thing will be certain – it never varies above a certain peak altitude, never drops a below a minimum altitude, and it always stays within those bounds. That band of permissible positions is its ***state space***. Within that state space, it can look quite complex, but it is always deterministic, the complex pattern generated by very simple Newtonian equations. Note that this example is a linear system. Its current state does not influence its future state, as the satellite is driven by a linearly timed schedule. You can correctly calculated the satellites exact position and velocity for any future time by applying those equations. The complex looking guilloché, analyzed by an inverse Fourier transform would reveal its harmonic or periodic

nature. Nonetheless, the basic principles of convergence, divergence, orbits, free energy, energy transfer, and complexity are the same for all dynamical systems, linear or non-linear. In discussions like this about energy and energy transfer, it is easy to see how thermodynamic concepts become applicable to chaotic non-linear systems, whether abstract or real.

The satellite example just given is a 2-body system, satellite and Earth, so it can be described precisely by ordinary equations and functions. In a system of 3 bodies, such as a planet with two moons, or an asteroid or even a man made satellite at a Lagrange point of Sun and Earth, position can never be exact, future position never precisely calculated. Since 3-body or n-body systems cannot be calculated as a linear function of time, they must be iterated, feeding forward to the approximate solution you seek, with as much precision or granularity that your computing resources permit. All such chaotic non-linear systems move in ways that are not harmonic and cannot be explained by Newtonian calculus (such as by a spring or gravitational equation). Nonetheless, the same thermodynamic principles apply. When a chaotic system is in a stable orbit, it continues on that chaotic attractor in the same way that an ideal spring (without internal energy dissipation) stays in its harmonic oscillation without needing new energy inputs. It is easy to understand that if I want to boost satellite orbit or spring oscillation, I need to put free energy in, by thrusters or stretching. For chaotic systems, changes of state and transitions between attractors can be increased by putting in virtual or analogous force or energy, by perturbation from outside stressors. Note that not all morphologies, datasets, or other outputs from complex systems are necessarily energy dependent. The guilloche described is not. Energy must be added to maintain the general attractor or state space, but the density or cycle number of the pattern depends on timing and alignment details that are governed without using energy. These patterns and morphological complexities are more a matter of the feedbacks and controls in the system, more a result their intrinsic or internal elements, rules, and dependencies. These are the "wave shapers" in the system, rather than free energy or moment shifts. Certain changes in internal rules or parameters can be equivalent to neutral energy redistribution and might change some of the precise iteration-by-iteration values of the system. However, the big changes, those affecting the general forms and morphologies of the attractor, and especially its basins, moments, and "centers of gravity" will depend on fundamental changes or shifts in dynamics, equivalent to adding or subtracting free energy.

If chaotic systems can have attractors that are essentially stable configurations representing certain energy levels, then moving between attractors may require potent perturbations. These can be seen in non-linear physiological systems such as the Wound. A wound that is healed, stable in a converged state, needs energy as new injury or disease flareup to diverge and reulcerate. Likewise, an actively sick divergent ulcerating wound needs potent non-trivial therapies to arrest disease and divergence and pull the system to at least an orbiting if not convergent attractor. A chronically impaired wound that has had the same orbit or clinical status for 24 months needs something potent to effect a fundamental alteration. Changing the type of dressing used may be a "wave shaper" that induces a bit more "granulation tissue" or a bit less periwound erythema, but without ever altering wound size. Initiating anti-immune or anticoagulant therapies that suppress the primary pathology, or injecting amnion or other living cell biologics to stimulate proliferation are the potent attractor shifting interventions that are analogous to adding free energy.

Think of complex systems and attractors as analogous to an egg crate. Attractors are basins of stability, the wells in which the eggs rest. A system will break away to another basin only if enough energy is put in to make the shift. This implies that there is some barrier to indiscriminate or easy shifting, like the dividers in the egg crate. If there is a barrier or threshold that must be crossed, the system will need a boost to elevate it above threshold. This concept, basins or wells of energy stability divided by threshold barriers, is common in nature. Consider certain exothermic chemical reactions or a nuclear fusion or an action potential in a nerve or muscle cell. An activation energy is required, something to boost the system to its threshold or trigger point, and then reaction is autonomous, releasing large amounts of free energy from broken bonds or fused nucleons or a propagating axon. The system has to go "over a hump", taking a bit of added energy to climb over, then yielding much larger amounts as it slides downhill, just as if it was falling in a gravitational field and giving up potential energy. Of course, once the system has settled into its new basin, there is no going back, at least not easily. If the reaction is nominally reversible, all of the dissipated energy has to be put back in again to boost it up over the now much higher hump. When chaotic systems hit stable attractors, it is as though they have gone over such an exothermic hump, giving up free energy, finding it "easier" to dwell where it is rather than move to another state or attractor. Energy inputs by extrinsic stressors are what can elevate the orbit again, and when the stressors are relieved, the system can settle back into whatever attractor or basin it can "thermodynamically" – or just plain "dynamically" – occupy for the current conditions.

As opposed to well known principles of chemistry and physiology, chaotic systems are generally not in equilibrium or steady state, but it can seem that way or analogies drawn. For example, when a logistic map settles into a bifurcated 2-value state, that could be a valid instance of equilibrium or steady state (see the links below for further information). Any n-value orbit that regularly returns to its multiple values could also be defined that way if you choose. For chaotic non-linear systems, the general dynamics are different than equilibrium or steady state, but they can be loosely associated for certain circumstances. Low energy wells and stable basins of attraction will seem steady or equilibrated when the system refuses to budge – like for a chronic wound that never really changes regardless what you do. When a chaotic system "gets stuck" in a low energy basin, it has effectively undergone an exothermic reaction, giving up free energy, dwelling at a point of low kelvin or basal energy. These basins are local minima, either in time or space: (1) time, the system may dwell there for a certain time, then applied energy or perturbations break that cycle and lift the orbit, or (2) space, in a complex physical system like the wound, there can be findings that indicate adjacent zones or strata are in different states. When the system has found a stable attractor or energy well, it can be difficult to displace it. This is why it can be so hard to make chronic and pathological CAP wounds heal. You are trying to break a stable attractor of a chaotic orbit. The system, the impaired wound, is in a state of dynamical stability where free energy is minimized, and displacement from that basin of attraction requires new energy or perturbation from the outside. Obviously, if the system with its own closed set of elements or actors has found a stable dynamic and wants to dwell there on a closed repetitive orbit, it just simply isn't going to go to another orbit until some potent agent from the outside comes in to persuade or force it to do something different. It is important to understand that for chronic pathological wounds, their clinical status may be undesirable, but the chronic persistent chaotic wound is a state of hard-to-break thermodynamic stability for that system.

Refer to the following links. This discussion has referenced additional concepts and models from non-linear dynamics that are not expounded on here. Further information about this subject as relates to wounds and other physiological systems can be read at these links:

The Physics and Pathology of Wounds
http://www.arimedica.com/presentations.htm#PPW3_100222_Maui

Part 1. The Wound as a System and a Controlled Machine.
http://www.arimedica.com/content/arimedica_wpp-1_wound%20control_gottlieb-me_maui-2010-0222.pdf
http://www.arimedica.com/content/arimedica_wpp-1_wound%20control_gottlieb-me_maui-2010-0222_annotated.pdf
Part 2. Auto-Immunopathy and the Intrinsic Disease of Wound Healing.
http://www.arimedica.com/content/arimedica_wpp-2_autoimmune%20&%20intrinsic_gottlieb-me_maui-2010-0222.pdf
http://www.arimedica.com/content/arimedica_wpp-2_autoimmune%20&%20intrinsic_gottlieb-me_maui-2010-0222_annotated.pdf
Part 3. Chronicity and the Physics of Wound Failure.
http://www.arimedica.com/content/arimedica_wpp-3_chronicity%20&%20failure_gottlieb-me_maui-2010-0222.pdf
http://www.arimedica.com/content/arimedica_wpp-3_chronicity%20&%20failure_gottlieb-me_maui-2010-0222_annotated.pdf

Non-Linear Systems, Chaos, and Coagulations. This discussion has relied heavily on references to wound physiology, but it is applicable to all complex physiological systems. Coagulation is one such system. Under healthy circumstances, it will dwell in a basin or attractor of dynamical and clinical stability, not clotting in vessels, but capable of a rapid shift to its convergent state of thrombosis. Illness in many different forms can dilute, deplete, or disrupt clotting elements and dynamics, allowing the system to diverge away from tuned thrombotic balance, i.e. hypocoagulable. Other disorders can lower the attractor's orbit, closer to ground or convergence, fewer degrees of freedom to regulate itself to the properly tuned balance, thus overly likely to clot, either spontaneous clotting without meaningful provocation, or a triggered response with an abnormally weak trigger, i.e., a state of hypercoagulability. The clinical implications of non-linearity and chaotic dynamics in the clotting system are discussed in the next panel. The concepts on this panel about non-linear dynamics, complexity, chaos, and attractors can be summarized:

Physiological processes are non-linear multi-control systems. Non-linear systems can have very complex behaviors, generally known as chaos.
Chaos is the behavior of non-linear and complex or multi-control dynamical systems.

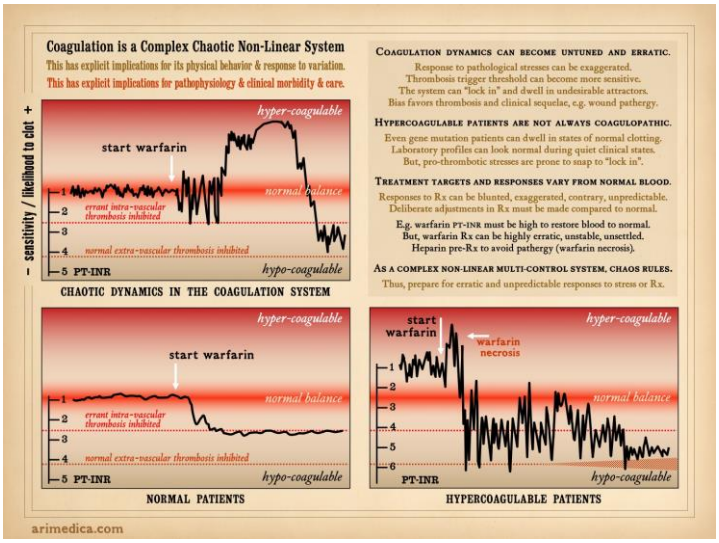
Regardless how complex the output or behavior, it arises from control and deterministic rules, so it is actually quite structured.
Such systems will occupy a state space, a range of permissible values, but dynamics within that space are not necessarily predictable or calculable.
Chaotic systems can seem orderly or they can be very sensitive to small perturbations or deltas causing big shifts in output (within the state space).

Non-linear systems can tend toward stable attractors, or they can be in excited states during episodes of perturbation or change.
Excited states represent stress or perturbation, adding to or withdrawing energy or information from the system.
For stable attractors, systems tend to "orbit", to dwell or return there.
Chaotic attractors are basins of dynamical stability, low energy wells that can be hard to break free from.

Control is what keeps biological systems from getting out of bounds, keeping a system within its operational range or state space.
Well controlled systems can absorb or suppress perturbations, but untuned or excited systems can fail or diverge with very small provocations.
In biological systems, a shift in the chaotic attractor or basin, or small perturbations, can result in undesirable clinical consequences.
Even when a chaotic biological attractor is clinically adverse, it is nonetheless a dynamically stable state and can be hard to alter or escape from.

Hypercoagulability is a Dynamical Disease, a disorder that might arise from variances in its constituent physical elements, but which has its manifest clinical consequences due to the altered operational dynamics of those elements as they interact in time within the framework of a complex n-body multi-control system.

***Humpty Dumpty**, illustration by English illustrator **Sir John Tenniel** (1820 – 1914), for **Through the Looking Glass** (chapter vi) by **Charles Lutwidge Dodgson** (1832-1898), better known by his pen name **Lewis Carroll**. Illustrating the concept that "you can't make an egg from egg salad", Humpty's great fall epitomizes the difficulties of sliding down an energy well – falling into a stable attractor – and not being able to climb out so easily, not even with all the king's horses and all the king's men.*



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Non-Linearity and Chaos in the Coagulation System

The complex non-linearity of the thrombotic system means it is tuned to a narrow band attractor, but it is never intrinsically stable. When system elements are altered, system tuning gets unbalanced, and responses to pathology or treatment can become disordered.

Coagulation, with many elements and feedbacks, is a complex non-linear dynamical n-body multi-control system. This implies chaos, with explicit implications for its functional behavior and responses to physiological, metabolic, and morbid changes in a patient (e.g., seen in variable levels of coagulation species). It also affects responses to treatment and patient care. Anticoagulants, especially warfarin, used in well controlled systems in stable low energy basins will be even-keeled and easy to regulate. When system elements are missing, altered, or dysfunctional, precise control can be lost, with exaggerated or contrary responses. This explains the often wild and hard-to-pin down prothrombin times when using warfarin in patients with hypercoagulable disorders.

Left upper pane. This is an abstracted concept of the coagulation system, graphed along the time domain. The function is the system's sensitivity to clotting, or likelihood that it will trigger and clot. The red mid band is normal coagulation balance, properly tuned so that blood will not clot in

normal vessels but will clot when exposed to "the outside". Above that, maroon is the increasing tendency to clot. In the lower bands of this zone, nearer to the tuned middle, the imbalance means greater sensitive to ordinary triggers, i.e. more likely "to fire" for triggers that are qualitatively proper and allowed but quantitatively not as potent as ordinarily required. This can also mean more of an exaggerated or amplified response to triggers. Higher in the upper zone, there is increasing likelihood that something normal within blood or blood vessels will be able to trigger the system, causing intravascular thrombosis. At the extreme high end, the risk is for spontaneous thrombosis due to inherent unbalance of the prime sequence clotting factors untriggered by morbidity or metabolic variances.

Below the balanced middle is the hypocoagulable zone, lesser tendency to clot. Near the middle, blood still clots properly, it just needs a stronger trigger than usual to initiate the action, but once triggered the response is normal. Farther away from the middle, clotting becomes less likely to occur, and more likely to be weak or impotent when it does happen. In the extreme, blood cannot clot. Note that these dynamics do not imply specific causes of failure. If blood categorically will not clot, it could be because (1) the blood has normal blood chemistry and factor levels, but they are critically blocked by an inhibitor such as giving high doses of heparin, or (2) the blood is depleted of clotting factors, e.g., severe liver disease or a dilutional state from hemorrhage and resuscitation.

The numerical scale to the left represents the PT-inr (prothrombin time, international normalized ratio, used to monitor warfarin therapy). When blood is normal, PT-inr should be 1.0. Consider a common use of warfarin, to prevent thrombosis for atrial fibrillation or a prosthetic heart valve. In those cases, blood is normal, coagulation is normal, inflammation is normal. These conditions create abnormal flows and surfaces that make the blood more prone than it should be to clot. Blood as a whole is normal, but "sensitivity to clot" over those relatively weak thrombogens is displaced a little above the balance line. The goal of prophylactic treatment would be to pull the system down by an equal amount, back to center balance. Using warfarin, adjustment of clotting profile to where errant intra-vascular thrombosis is inhibited would be at a PT-inr approximately 2.5. Elsewhere in the body not over those surfaces, at that level, clotting might take a more potent stimulus to trigger, but "seeing" an injury would still activate thrombosis, meaning that doing surgery at that PT level would not usually be perceptible to the surgeon. If anticoagulant therapy was more aggressive, the PT-inr would prolong further, "thinning" the blood such that bleeding times would prolong and that coagulation capacity or reserve for large injuries would be diminished. With yet greater anticoagulant effect, eventually even normal coagulation triggered by collagen and tissue thromboplastins is inhibited, perhaps at a PT-inr value between 4 and 5, beyond which the blood is "broken".

The black trace is a hypothetical waveform of coagulation balance, sensitivity to clot. At standby normal conditions, it is on the center line. However, it is not an invariant flat line. Due to the complex non-linear multi-control nature of the system, it will tend to vary back and forth, never too far high or low but never exactly predictable between the upper and lower bounds, i.e., always having chaotic variations within its state space. In the center is a zone where the trace becomes erratic or exaggerated, elevated dynamics indicative of some type of stress or perturbation. For example, it could be a patient starting warfarin at a sub-therapeutic dose. Next to the right is a zone going high, example being the baseline status of a patient with a hypercoagulable state, where the baseline sensitivity is high but also has exaggerated moment-to-moment variability. Right of that is a zone of further likelihood of thrombosis, for example a hypercoagulable patient starting warfarin or estrogens. At the right end is a zone where coagulation potential has dropped low, where average PT-inr is in a nominal therapeutic range but erratic, such as hypercoagulable patient who has finally found an workable warfarin dosing scheme.

Left lower pane. The upper pane showed, for the sake of illustration, a smattering of abstract conditions. This pane shows the empiric coagulation dynamics of a single idealized patient under the specific condition of having normal baseline blood and clotting while being anticoagulated to treat atrial fibrillation. Since this patient is normal to begin with, coagulation dynamics are centered. There is some degree of normal non-linear chaotic variance, but not exaggerated. For instance, if daily or hourly measures were made of fibrinogen or prothrombin time (reported to two decimal places), this is how things would probably look. When warfarin is started, the PT-inr trace moves down (higher inr value). There are some irregular and exaggerated early variances, as expected for a non-linear multi-control system, but the envelope or moving average is an exponential transition to the new level as expected. The given clinical indication typically warrants that PT-inr be managed at a level of 2.0-2.5, and in this idealized case, that level is achieved without much deviation from a smooth course. This does not imply that the treating physician simply picked a given dose and that was that. Warfarin management is itself a closed loop control system that requires periodic measurement of PT-inr (system feedback), comparison to target value (system reference), and then adjustments via a new prescription (system controller). Whatever went on "behind the scenes", the PT-inr value hit its target relatively smoothly and then stayed stable for a prolonged period. In a healthy coagulation system with all of its elements healthy and properly tuned, without extrinsic stresses and offsets, the single perturbation of giving warfarin can be absorbed or accommodated, the physiological adjustment made without extraordinary chaotic variability. The entire dynamical system has shifted to a new level or system control reference in which triggering thrombosis will now require a more potent stimulus than its natural set point. At proper therapeutic levels, the thrombogenicity of altered flow in the fibrillating atrium is no longer sufficiently potent to trigger intravascular thrombosis, but injury to a vessel exposing collagen or tissue factor remains an effective trigger.

Right lower pane. This tracing is for a similar situation except that the patient has a hypercoagulable disorder. Warfarin might be starting for the same indication of coincidental atrial fibrillation, but it might also be for a complication of the hypercoagulability such as venous thrombosis with pulmonary embolism. On the left side, this patient starts in the hypercoagulable space above the center balance. Baseline coagulation dynamics are also more erratic than normal, a consequence of the system already being unbalanced by one errant species forcing an over-reaction of compensatory reflexes from other controllers throughout the system. Recall that prothrombin time is not a global measure of coagulation, just the best verified tool to be used for warfarin monitoring. Most likely this patient has a normal PT-inr of 1 despite aggregate clotting dynamics being altered. This means that monitoring warfarin therapy needs to be adjusted, as shown by an upward offset of the numerical scale. When warfarin starts, which is an added perturbation in the system, short term dynamics become more erratic. The tracing shows that soon after warfarin start, that clotting sensitivity rises a little, more likely to clot. This is when and why that the syndrome of warfarin necrosis becomes a risk (see illustration on next panel). This complication, in which indiscriminate skin necrosis can occur on any part of the body, typically happens in the early phases of warfarin therapy. Warfarin inhibits vitamin K which in turn inhibits liver production of plasma clotting proteins. Warfarin necrosis is attributed to a relative imbalance of these plasma factors as they start to fall. For example, proteins C & S (but not antithrombin-3) are vitamin K dependent, and if they deplete faster than the procoagulant or main sequence proteins, then clotting can be overdriven. That is why warfarin necrosis is expected within the first few weeks of therapy, and not afterward when the warfarin doses and readjusted prothrombin times are stable and plasma factors

are more uniformly suppressed. Warfarin necrosis is not so apt to happen in people with prior normal clotting profiles. It is more likely in people who are already more sensitive to thrombosis or more chaotic due to a hypercoagulable tendency or disorder. Any patient exhibiting warfarin necrosis should be screened or worked up for a hypercoagulable disorder.

When the anticoagulant effects of warfarin start to take hold, the drift down to target prothrombin times is more erratic than for normal people, and staying at an adjusted level is harder, the PT-inr tending to jump around. This is an oft heard complaint from patients, "My doctor put me on Coumadin for that pulmonary embolism three years ago, but the INR was all over the place, and the doses kept having to go up and down, so it was safer to stop it." If you initiate therapy yourself with one of your patients, you will likely observe the same. (Fortunately, newer classes of drugs such as apixaban and dabigatran circumvent this problem by directly inhibiting thrombin without going through the circuitous pharmacology of warfarin and vitamin K). These erratic warfarin dynamics "at target" are reflected in the right side of the tracing as PT-inr values jump around. Recall that therapy dynamics for hypercoagulable patients are a bit different than for normal patients. You are not "thinning" normal blood, rather restoring balance to normal. Of course, if the patient is being treated for atrial fibrillation or other thrombogenic condition, anticoagulation therapy should be additive for the restoration to normal balance plus a little "thinning". Just like for any normal person getting anticoagulated, therapy should try and pull sensitivity-to-clot into that range below the red baseline of normal clotting to the line where errant intravascular thrombosis is inhibited. As seen in the tracing, tendency in hypercoagulable patients will be to wander high and low, risking getting below the line where normal reactive stop-bleeding thrombosis is inhibited, or else popping back up to a state where intravascular thrombosis is again possible. Maintaining a smooth relatively well regulated therapeutic band is often difficult in patients with hypercoagulable disorders. Notice how the PT-inr needs to be recalibrated for these diseases. These patients are hypercoagulable with an INR of 1. They are of normal coagulation balance when INR is about 1½ - 2½. Normal degrees of therapeutic anticoagulation that suppress intravascular thrombosis are reached at values of 2½ – 4 (the precise values or ranges will vary slightly for individual patients and problems). The problem for these patients is that the INR can get quite prolonged, maybe 6 – 7, yet patients will still have ongoing clinical signs or direct physical findings of hypercoagulability, such as repetitive catheter thrombosis or rapid clotting or brief bleeding times during surgery. For these patients, the prothrombin time becomes uninterpretable, and warfarin, with its odd and potentially dangerous pharmacokinetics, becomes impossible to assess and be certain of its effect. In prior years when dicoumarol drugs and heparin were the only options, this was problematic, but nowadays, with direct factor inhibitors and low molecular weight heparins, these are convenient and effective options for treating patients without warfarin.

Clinical implications of non-linear dynamics and chaos in the hypercoagulability disorders. Nature is what it is. Physiology experimentation and teaching, and the traditional medical curriculum, have not kept pace with advancements in the other physical sciences that appreciate that complexity is the way the universe actually operates. If non-linear dynamics and chaos seem like arcane subjects beyond or outside the domain of medicine, it is only because physiology and medical teaching remain mired in 19th century concepts of "homeostasis", "steady state", and the preeminence of chemistry in biological systems. Blood coagulation is a complex n-body system. Like all physiological systems that must maintain a certain operating range in order to function and survive, it has multiple levels of feedback and reference driven controls that keep the system in its proper state space. In its healthy state, the entire system is well regulated, meaning that moment-to-moment variances go unnoticed, and responses to major perturbation are often absorbed or corrected before anyone is the wiser. When perturbation exceeds the capacity of the system to respond, or the system itself is damaged or dysfunctional in some way, then clinical consequences become manifest.

Much of the morbid dynamics relate to "degrees of freedom" to react and respond. A perfectly healthy system has a lot of latitude to endure perturbation, because multiple layers of healthy control will correct a transient stress or imbalance. If the system already has something wrong, it might not necessarily appear so outwardly. Feedbacks and controllers in the system will have adapted to the imbalance so that the net system output is normal or the error signal related to the system reference has been compensated, and the subject will seem healthy. However, in those cases, an additional small perturbation from some illness or injury might not be able to get absorbed, and clinically adverse manifestations appear, either as hypocoagulable bleeding or else hypercoagulable thrombosis within blood vessels. By way of analogy, consider an airplane that has lost one of its flight control surfaces, such as a stuck aileron. It will cause the plane to roll and turn, but the pilot could compensate with the rudder or differential engine power, and the plane can stay controlled and on course to the airport. What happens though if another control fails, if the rudder jams or an engine is lost (the system itself is further damaged), or if a strong crosswind is encountered (external perturbation)? With the remaining control systems already saturated at their operational limits, the additional stress may exceed the capacity of the system to compensate and correct. Failure and catastrophe are at risk. In patients, with hypercoagulable disorders, they already have one error in the system, and other subsystems are compensating, but this does not leave a lot of room for variances. When other perturbations or stresses come along, functioning compensators or controllers must overtax their operational capacities, and the internal dynamics of the system start to feel unusual pushes and pulls, resulting in increased swings and instabilities which in turn stress the inputs and responses of other connected subsystems. Aside from the obvious states of overt hypocoagulability with bleeding or overt hypercoagulability with intravascular thrombosis, other "in between" signs and therapeutic principles likely to be encountered clinically include the following.

As a complex non-linear multi-control system, chaos rules. Hypercoagulable thrombosis is a "dynamical disease", thus, prepare for erratic and unpredictable responses to stress or treatment. As with all chaotic systems, small variances (starting conditions) and perturbations in the system can have small or major effects on the output, either continuously or intermittently, due to age, chronic disease and comorbidities, drugs and therapies, and acute illness and injury. These factors 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. They can also make the system less sensitive, inducing an anticoagulated state which might be desirable, but risking going too far and causing hemorrhagic complications. They can also upset the response to treatment, as is seen so often in trying to regulate warfarin.

Coagulation dynamics can become untuned and erratic. In hypercoagulable states, the response to injury and pathological stresses can be exaggerated. The system becomes biased to favor thrombosis and clinical sequelae such as overt thrombi or occult events such as wound pathergy. The thrombosis trigger threshold is more sensitive, meaning that thrombotic events and complications can be more frequent or occur in unlikely or unexpected circumstances or in response to innocent therapeutic interventions. Furthermore, once such situations get riled up, they can enter a dynamically self-sustaining attractor that "locks in" and dwells in that clinically undesirable state, a state that will not regress spontaneously and

requires explicit treatment. The treatment can be as simple as starting a continuous heparin infusion, but without such, progressive thrombosis and infarcts will continue.

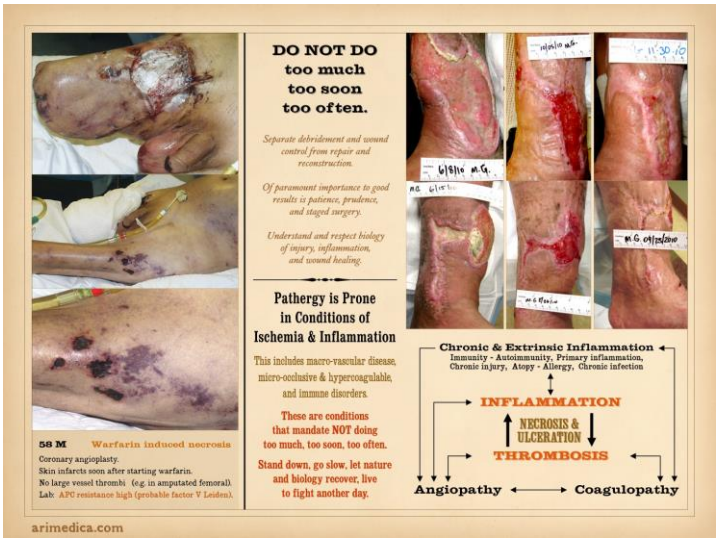
Hypercoagulable patients are not always coagulopathic. Because of the regulated controls throughout the system, hypercoagulable stresses and offsets can be compensated for. This means that a person can have a hypercoagulable species or variance or bias, but clinically it will be unnoticed and uncomplicated unless some additional stress is superimposed. This is true even for those with immutable inborn errors such as gene mutations such as factor V Leiden. On normal healthy days, they can dwell in states of apparently normal clotting. Even laboratory profiles (using just ordinary tests that can be ordered via the clinical lab) can look normal during quiet clinical states. However, these are still dangerous hidden gremlins in the system, and once a hyperthrombotic profile is "charged up", snapped into a beyond-threshold state, clinical sequelae can happen, and the system risks "locking in".

Treatment targets and responses vary from normal blood. In hypercoagulable patients, responses to treatment can be blunted, exaggerated, contrary, paradoxical, unpredictable, and in other ways at variance from normal, predicted, and expected responses. A key tipoff to undiagnosed hypercoagulable states is the occurrence of more thrombotic events despite being on nominally therapeutic levels of anticoagulant mediations. With these disorders, deliberate adjustments in therapy must be made compared to normal people and drug management parameters. Remember, that anticoagulating such patients to ordinary targets (e.g. getting the PT-inr to 2) may simply restore their gross clotting profile to normal, and that genuine anticoagulation that prevents errant intravascular thrombosis might not occur until the INR is 3 – 4. The problem is that the therapy itself can be highly erratic, unstable, and unsettled. Non-hypercoagulable patients who are placed on warfarin can be regulated fairly easily (e.g. atrial fibrillation, vascular surgery), but hypercoagulable patients can have an unpredictable roller coaster ride with warfarin. The treatment itself risks complications that are not so likely to occur in normal non-coagulopathic patients, such as warfarin necrosis or recurring thrombosis while on therapy. This has additional implications for treatment that may not be relevant for normal non-coagulopathic patients.

Additional treatment implications. It is important to mention the final pathway of clotting and how the anticoagulant drugs work. The coagulation control system works to maintain a balance in the plasma's state of readiness and response to control bleeding, never clotting in vessels, but clotting almost immediately upon provocation. The actual clot results from conversion of fibrinogen to fibrin, catalyzed by thrombin which in turn was catalyzed from prothrombin by the antecedent steps in the entire process. All back and forth, up and down, push and pull regulatory processes in the system are meant to control the lead up to thrombin then fibrinogen conversion. When clotting does occur, fibrinogen is consumed. It can be replenished rapidly, part of the grand overall control system, but the actual action is a shunt or grounded branch of the main control loop, a side circuit that is the actual effector of the clot that stops bleeding. Turn that off, and clotting stops. ***Warfarin*** works far upstream in the system. It diminishes concentration of many of the plasma factors, but it does not at any point block or interrupt the control loop or clotting cascade. When warfarin therapy is properly tuned, plasma factors are diluted but still present. Furthermore, feedback regulated controls in the system all still work, so compensatory processes can keep the blood functional in most regards. This means that clotting is attenuated, quantitatively weakened but qualitatively still correct in many ways, which is why warfarin anticoagulated blood at proper PT-inr's is usually well behaved and clots properly when doing surgery. Warfarin is a proven drug, very effective for therapeutic anticoagulation in most circumstances, but by working far upstream, it leaves room for or creates potential instabilities and chaos. ***Heparin*** works instead by binding to antithrombin-III, one of the endogenous anticoagulants which works by inhibiting thrombin's ability to convert fibrinogen. The bioactivity of AT-3 is amplified many fold by binding to heparin. If thrombin cannot do its job, then there is likely no fibrin and no clot, but not strictly so. Thrombin is not the end of the circuit, fibrin is, so other controls and regulators can sneak around it and restore some fibrin conversion. Even so, heparin is a very effective anticoagulant even if not completely perfect. When present, it is in many ways like an on-off switch that prevents the final clot. The effect is of course concentration dependent, and by using proper doses thrombosis is inhibited, not categorically broken, although that is effectively so if enough heparin is given. The value of heparin is that by working so pointedly so far downstream, the system has few options to restore coagulability. It is also "gentler" on the whole system, not inducing upstream perturbations which instigate a multitude of compensatory responses. Unlike warfarin, the effects of heparin are in many ways "invisible" to the rest of the system, an "end of the line hijacker" that precludes opportunities for counter-regulation. The same is true for the newer class of ***direct thrombin inhibitors*** such as apixaban and similar. This makes heparin and the thrombin inhibitors valuable to protect against warfarin side effects and other transient perturbations and transitions within the system. In patients where chaotic warfarin dynamics are anticipated or put the patient at risk, incurring transient risks of thrombosis, necrosis, and wound pathergy, heparin can be the safety drug which protects that transition, preventing clotting until changes in warfarin dosing have a chance to settle into a stable new state.

Adjunct treatment implications. This discussion has emphasized the importance of anticoagulants to interrupt the pathological dynamics and prevent thrombosis. However, treatment is not always so simple. There are times when, not only will active infarcts and ulceration and other signs of thrombosis continue while anticoagulated, but the patient will simultaneously have hemorrhagic bleeding complications elsewhere, e.g. epistaxis or hematuria or hematemesis even while thrombo-infarctive leg ulcers progress. The blood is over-anticoagulated with respect to basal thrombotic balance, but is still hypercoagulable as it passes through zones of injury and inflammation. In such cases, odds are that the pathology is a mix of hypercoagulopathy and autoimmunity. Treating the inflammatory and immune components is then essential. Typically this is done with steroids or other anti-immune agents. Even then, some patients will have refractory thrombosis and persistent wounds. For such patients, plasma pheresis or plasma exchange can solve the problem. This modality will scrub the blood of the antiphospholipid antibodies, other immune procoagulants, and a variety of other immune-inflammatory chemistry. It can have remarkable effects not only to settle inflammation and systemic instabilities, but to directly improve or reverse the hypercoagulable state, and thereby to induce healing in the problematic wounds.

Illustration. *Seen on the left side of the next panel. This is a 58 year old man who had an otherwise uncomplicated coronary artery angioplasty. About a week or two after the procedure and starting warfarin, He suddenly developed acute multifocal vascular stasis and infarction of the skin. Multiple other incidental indicators of multisystem acute morbidity imply that ischemia and infarcts were possibly happening elsewhere. Extensive involvement of the right lower extremity necessitated amputation, and the surgeon commented on the remarkable finding that the femoral vessels were normal and there was no thrombus in the large arteries. The photographs confirm the signs of cyanotic vascular stasis and pure thrombo-infarctive pattern of necrosis. Laboratory workup showed that he was APC resistant, implying most likely factor V Leiden. This case fits perfectly the timeline and physical and pathological findings of warfarin necrosis.*



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Locked-in Attractor

When the inflammation-thrombosis attractor locks to a state of mutual sustentation, then wound pathergy, necrosis, and lysis are assured. More surgery will have results contrary to intent. That is the time to suspend surgery and control inflammation and coagulation.

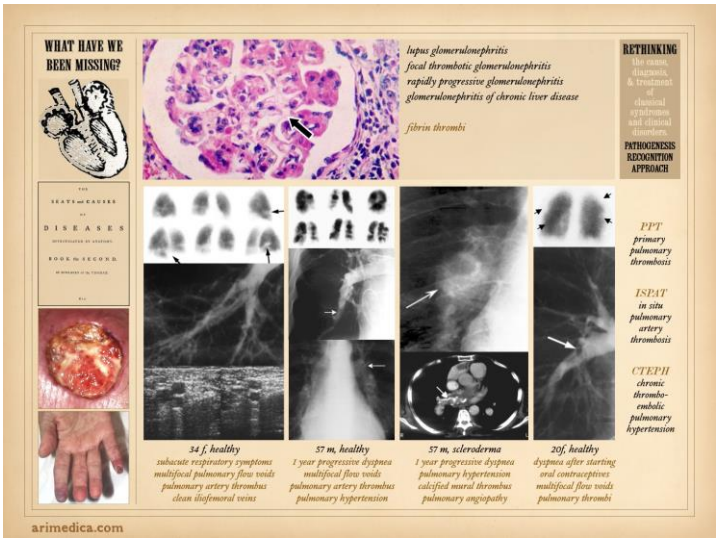
Wound pathergy and complications of surgery often occur because of the mutual ramp-up of coagulation and inflammation. A mistake is to keep operating and making the problem worse, especially when there are inflammatory, immunopathic, vaso-occlusive, and coagulopathic factors at work. Do not do too much, too soon, too often, or the stability of a clinically undesirable attractor will strengthen and lock in.

*[**Left.** This is an illustration of warfarin necrosis, a carryover from and discussed on the preceding panel.]*

Right. This is a 66 year old man with complex fracture of left ankle with overlying skin injury. Fracture was reduced and fixated with hardware. The bones healed and were inherently uncomplicated, in part because initial soft tissue coverage over fracture and hardware successfully protected them. However, wounds remained open at skin level. Rather than be prudent and wait to close the skin when eligible to be successful, instead the patient 15 operations under anesthesia in 18 days. This quest included flaps, grafts, and other failed closures. With each event, edema, inflammation, and skin and wound infarcts got worse. If wound closure surgery fails once, a second try is often fair after proper preparation. A third try might be justified with compelling reasons. After that, chances of successful short term closure is essentially impossible. When seen for first consultation, there was intense inflammation, edema, and drainage throughout the wound and leg. There had been no program of effective hygienic topical wound care. There had been no compression or other edema control modalities. Through 15 cut-and-sew procedures, nothing had been done to alleviate or control the repetitive trauma and inflammation that instigated or perpetuated the inflammatory state. Instead, the cure was worse than the disease, the patient getting worse with each failed intervention. In fact, there was no disease other than the repetitive surgery and lack of basic wound care. The patient had good pulses. History and lab screens were negative for autoimmune and hypercoagulable and related disorders. The problem was strictly one of too much trauma causing too much inflammation with secondary adverse effects on the wound. The photo series starts ***left*** with lateral (***top***) and medial (***bottom***) views of the distal leg and ankle. The first view is the earliest available picture, showing the large size of the wounds, already improved after a week or two of topical hygiene, anti-inflammatory control, and compression and edema control. The ***middle*** set shows the progress after several weeks of the same care. Some skin grafts to expedite closure might have been valid at this point, but the patient, seeing progress, was opposed to any further procedures. The ***right*** set shows the medial and anterior aspects healed, with a remaining open area slower to heal, as expected, over the lateral margin of the fibula.

The problem here was a consequence of the non-linear mutual effects of inflammation and thrombosis, the loop of pathology that traps necrosis and inflammation in the middle. Repetitive injury stirs up these responses to injury. Think of this system like the orbital or oscillatory systems discussed previously. In a system where thrombosis and inflammation have a sustentative effect on each other, the wound system is orbiting in a certain chaotic state. If there is no further injury, and if the patient is otherwise healthy, the system will have the necessary reserve in its controllers to wrangle the wound back into control, and it should start to improve, to give up dynamical energy and converge toward closure. If the subject is healthy, but conditions are adverse, then it might not converge. Non-specific minor promotors of inflammation or thrombosis, such as delinquent wound care, can add small amounts of provocation or effective energy to the system to offset convergent losses, thereby keeping the wound as is, the same as keeping a clock ticking or an orbit on altitude by the addition of small amounts of energy to offset friction losses. Major promotors of inflammation and thrombosis, such as new trauma or surgery can add enough new energy to raise the orbit, a more active or divergent wound that gets worse. If the patient is not healthy, instead having disorders of circulation, immunity, or coagulopathy, then these factors amplify the effects of further injury, or damage system controllers, all tending to aggravate the wound and make it worse. Doing too much surgery, too soon, too often is the sustentative stress that will perpetuate the wound. It is to be avoided in anyone, but it becomes especially pernicious in those with background disorders of inflammation and thrombosis. While these comments are oriented to the wound, they apply equally to the thrombosis-coagulation system in which trauma and inflammation are the provocative factors. (And, consistent with all proper 3-body systems, trauma and coagulation are the provocative factors that will sustain inflammation.)

Too much too soon too often. In this example, there was nothing wrong with the patient other than too much surgery, too soon, too often, for no mandatory indication nor any other valid reason. He got worse by doing more and more surgery faster and faster. He got better by doing no surgery and instead doing simple treatments that corrected basic adverse wound conditions of edema and inflammation. The question that must now be asked is this: if this can happen to a reasonably healthy patient just by doing more and more when less and less is required, then how little of "more and more" is needed to create problems when the patient is unhealthy, afflicted by conditions of ischemia and inflammation, disorders of immunity, thrombosis, circulation and related factors which cause, sustain, and perpetuate these adverse events? In contrast, when a surgeon does follow the rules and does not violate any of these principles, yet the wound or flaps or surgery undergo necrosis and ulceration, wound pathergy, why? What caused these unexpected adverse events, what are the risks for more trouble, and how can problems be corrected or circumvented? Now, substitute "hypercoagulability" for "wound getting worse", and these comments remain valid. When treating these decompensated systems, do not do too much, too soon, too often. Understand and respect the biology of injury, inflammation, coagulation, and wound healing. Stand down, go slow, let nature and biology recover, and live to fight another day. Separate debridement and wound control activities from repair and reconstruction procedures. Of paramount importance to good results is patience, prudence, and staged surgery. If the problem is not so much one of ulceration but rather infarction, systemic thrombosis, other signs of hypercoagulability, and even signs of morbid hypocoagulability, the same principles apply to abate the provocative causes.



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Hypercoagulability – Misunderstood and Overlooked Implications

If you do not know or recognize hypercoagulability, then you cannot properly diagnose its clinical manifestations. Instead, you make diagnoses based on your extant framework of knowledge, but they will be false, and the ensuing treatments will be false or ineffective.

Pictured are Da Vinci's heart, with its atria, valves, and central vessels grotesquely misdrawn, and Morgagni's De Sedibus which observed but failed "to see" pre-mortem intravascular thrombosis, and which also failed to see stromal diseases in favor of purely organ originated pathology. Pictured below that are examples from panels 18 & 19, a young woman with lupus whose so called "Raynaud's" was really antiphospholipid hypercoagulopathy, likewise for the young man who suffered the misery of many failed procedures and iatrogenic complications as his known lupus was not equated to an antiphospholipid antibody syndrome. What else have we been missing?

Panel 33 presented a brief history of the autoimmune cvd-ctd's and the first awareness of hypercoagulable disorders. Recall Hughes' landmark 1983 paper that described APLAS, ***Thrombosis, abortion, cerebral disease, and the lupus anticoagulant***. The title itself hints at the Hypercoagulable Syndrome as presented here, with thrombosis, abortion, and an inference to lupus. Family history is not mentioned, nor wounds, but neurological disease is. Indeed, if such a patient presented to a Neurology practice rather than a Wound-Surgery practice, one might validly substitute cerebral disease for wounds and pathergy. In those years circa 1940-1990 when concepts about those vague and non-obvious disorders of systemic lupus erythematosus, systemic collagen diseases, auto-immunity, and antiphospholipid antibodies were starting to take form then crystallize, there were many papers describing many clinical features of those disorders, features which at the time were hard to place in a pathological theory or a nosological schema of disease. Nonetheless, reports recognized that patients diagnosed with syphilis or seizures or multiple sclerosis actually had wrong diagnoses, that immune factors were the culprit, and even if hypercoagulability per se was not recognized, the presence of an abnormal VDRL or antiphospholipid antibodies was. It was recognized that some people with lupus-associated renal failure had histological signs of autoimmune glomerulopathy, but others did not. In 1924, in the *Archives of Internal Medicine*, ***Emanuel Libman*** (1872-1946) and ***Benjamin Sacks*** (1896-1971), published another seminal paper, ***A Hitherto Undescribed Form of Valvular and Mural Endocarditis***. Libman-Sacks endocarditis was a mystery disease then as it could not be ascribed to infections and post-streptococcal status. By mid century, it had been equated to lupus, and an association with antiphospholipids and anticardiolipins was noted by 1985. Embolic strokes have long been reported as a complication of Libman-Sacks carditis, and modern findings that antiphospholipid antibodies are abundant in the affected valvular lesions provides an explanation for the thromboembolic events. Other papers reported on multiple pulmonary thrombosis leading to pulmonary hypertension. Pathology studies established the occurrence of primary non-embolic pulmonary thrombosis. Papers reported on various other unexpected disorders associated with auto-immunity, or on complications associated with lupus, or on clinical events associated with phospholipid antibodies. Before 1983, these odd observations were abundant but never connected. Over the next 20 years, it became possible to see the interconnections between the antibodies, the autoimmunity, the coagulopathy, the autoimmune syndromic features, the hypercoagulable syndromic features, and their mutual interdependence. Many signs and symptoms and oddball clinical syndromes now started to make sense, especially when autoimmunity and vasculopathy could rationally be excluded from the diagnosis and instead a positive identification of a hypercoagulable disorder could be established.

(An historical sidebar here is of interest, inasmuch as this presentation is coming from the author's home state of Arizona. Benjamin Sacks attended medical school at Johns Hopkins University (Baltimore), then had his career at Mount Sinai Hospital (New York City). Forced to retire from practice by health issues, he moved to Los Angeles and became the medical technical advisor for many Hollywood films. He developed an interest in the history of the United States southwest, especially Arizona territorial history. In 1964, he published an award winning book, "Be It Enacted: the Creation of the Territory of Arizona". His vast library of materials on Arizona history became a premiere resource of the Arizona Historical Foundation which he helped found in 1959 (absorbed into the Arizona Historical Society in 2012). Throughout his career, he was praised equally for the degree of detail and precision that he brought to both his medical and historical scholarship.)

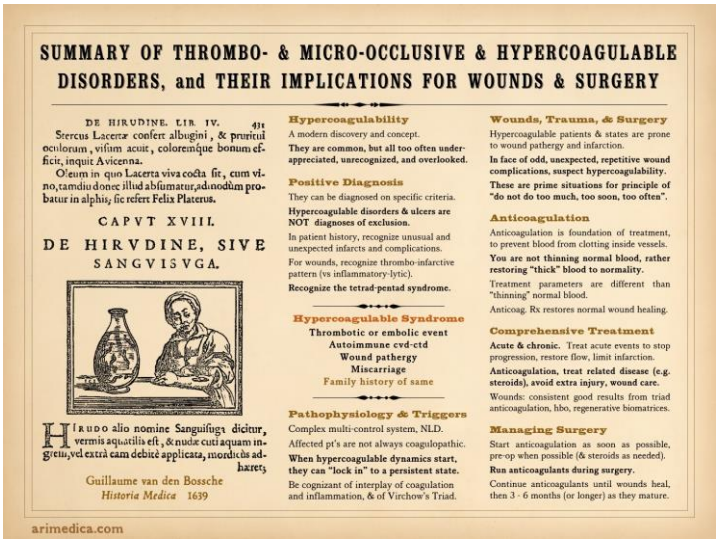
Old ideas about the pathogenesis of certain disorders, especially when they did not fit with verifiable theories of disease or direct exam (be it physical, laboratory, post-mortem, or histological) could now be discarded in favor of rational ideas that fit the observed facts. This begs two important questions. (1) What other problematic diseases or syndromes that seem to defy customary diagnosis or treatments are also due to micro-occlusive hypercoagulopathies as the primary disorder? (2) Why is it that, with ample opportunities to learn or know about this, the subject remains oddly unknown and arcane among the majority of physicians? Consider the examples illustrated here. **(1)** A 34 year old woman, previously healthy, presents with subacute respiratory symptoms. Pulmonary perfusion scan shows multifocal pulmonary flow voids. Angiograms show pulmonary artery thrombus. Peripheral doppler shows clean iliofemoral veins. The implication of multifocal occlusion without signs of a venous source is that this is primary intrapulmonary thrombosis. **(2)** A 57 year old man, previously healthy, has progressive dyspnea developing over 1 year. Pulmonary hypertension is diagnosed. Pulmonary perfusion scan shows multifocal pulmonary flow voids. Angiograms show pulmonary artery thrombus. Same as for case 1, the implication is for primary intrapulmonary thrombosis, in turn implying hypercoagulopathy. **(3)** A 57 year old man with scleroderma has progressive dyspnea developing over 1 year. Pulmonary hypertension is present. Angiograms and CT show pulmonary angiopathy with calcified mural thrombus. Scleroderma implies intrinsic angiopathy, but calcific mural thrombus implicates primary in situ pulmonary thrombosis. **(4)** A 20 year old woman, previously healthy, becomes dyspneic after starting oral contraceptives. Pulmonary perfusion scan shows multifocal pulmonary flow voids. Angiograms show pulmonary artery mural thrombus. The same indicators are there of multifocal in situ thrombosis.

Primary pulmonary thrombosis as identified in pathology studies has been recognized since the 1940's. In recent years, especially with increasing interest in pulmonary hypertension and the ready availability of limited or non-invasive imaging, the nomenclature of pulmonary thrombosis and hypertension have expanded to include ***PPT*** primary pulmonary thrombosis, ***ISPAT*** in situ pulmonary artery thrombosis, and ***CTEPH*** chronic thrombo-embolic pulmonary hypertension. These are the patients who have "dvt" despite having no evidence of peripheral thrombosis, or have continuing and multifocal "emboli" despite anticoagulant treatment, or despite having had placement of a vena cava filter. What heretofore was all too easily lumped under one designation of "venous thrombosis and pulmonary embolism" is much broader than that. Even for patients who did have deep venous thrombosis, why did they have it?, or why do they have recurring dvt's despite treatment? There are dvt's and genuine pulmonary emboli that occur for various reasons even when the blood clotting profile is intrinsically normal, but unless a reason can be identified such as trauma along the femoral veins, a hypercoagulable state should be entertained, especially for odd, recurrent, refractory events, or for patients with a suggestive history such as a high score for the Hypercoagulable Syndrome.

Pictured is a renal glomerulus in a patient with lupus. It is missing the immune crescents that textbooks describe as the hallmark feature of lupus glomerulonephritis. There is also the syndrome of ***RPGN***, rapidly progressive glomerulonephritis. In half or more of people it is a crescenteric immune nephritis associated with lupus or Goodpasture's syndrome or other known immune disorder. However, a large percentage of rpgn cases do not have crescents or signs of immune activity. Instead, they can have ***fibrin thrombi visible in the glomerulus***, as indicated in this image (arrow). This profile seems analogous or equated with other clinical profiles such as ***focal thrombotic glomerulonephritis***, ***renal thrombotic microangiopathy TMA***, and the ***glomerulonephritis of chronic liver disease***.

Notice how real disease and pathophysiology come into conflict with conventional teachings and disease nosology. In the style of Morgagni, we assume that if the kidney goes bad, it is kidney disease. If the liver or lung fails, it is liver or lung disease. The idea of poly- or trans-organ pathology mediated by diffuse disorders of the body's infrastructure systems is a relatively new concept. Paul Klemperer was one of the first to advance the idea in his 1942 paper on lupus and collagen diseases (see panel 33). Goodpasture's pneumorenal syndrome, affecting lungs and kidneys is another example of multi-organ pathology due to systemic immune events. However, pathologist ***Ernest Goodpasture*** (1886-1960) described the syndrome in ***1919*** studying cases during that infamous flu pandemic, but he knew not of anti-glomerular basement membrane antibodies, bred by a systemic autoimmunity, a discovery that would await a paper by ***RA Lerner*** at al in ***1967***. Diseases of the immune and inflammatory systems, of the generic stroma of the body, of blood vessels which transport blood, and of the blood itself including its coagulation system are the infrastructure disorders that can cause acute or active pathologies in remote and disparate organs. Hypercoagulability is not the only means of micro-occlusion and micro-infarction, nor the only means of disseminated or multi-focal pathology, but it is one of them, and all are important. Bit by bit over the past century we have come to appreciate the pervasive and prevalent implications of immune and autoimmune disorders, including the "classic" connective tissue cvd-ctd's, immune complex and deposition disorders (e.g., Goodpasture's), crossover immunity (e.g., rheumatic fever), organ transplantation, and many others. Appreciation of the pervasive implications of micro-occlusive disorders has lagged, especially for the hypercoagulable disorders which, unlike leukemias and hemoglobinopathies, are not so readily appreciated by simply looking under the microscope.

It is easy now to look back on old patients and realize they would have done better had we then understood hypercoagulability. Remember that hypercoagulability, based in blood which circulates the whole body, can affect nearly every organ or tissue. The astute clinician must be ready to make an inferential or deductive diagnosis of such when some odd syndrome or presentation defies other explanations, especially with supportive exam and history such as the Hypercoagulable Syndrome. Repetitive pulmonary thrombosis and pulmonary hypertension should not be overlooked in favor of the convenient freshman diagnosis of "pulmonary embolism" especially when there is no evidence of venous thrombosis. If rpgn occurs in a lupus patient who has no evidence of immune glomerulonephritis, then hypercoagulable antiphospholipid antibodies are likely. For them, perhaps chronic renal failure and the eventual need for dialysis and transplantation can be prevented by anticoagulation. Remember, for years we "knew" that Raynaud's 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 more recently even the lupus itself, even though there was no evidence nor did the ulcers improve with those specific therapies. Now we know otherwise. What have we been missing? What are we still missing? We must rethink the cause, diagnosis, and treatment of classical syndromes and clinical disorders, not the diseases per se, because nature is what it is, but our understanding of those conditions and how to make the correct diagnosis and render correct care.



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Summary of Thrombo- & Micro-Occlusive and Hypercoagulable Disorders, and Their Implications for Wounds & Surgery

To summarize the thrombo- and micro-occlusive and hypercoagulable disorders, crucial points to remember are that they can be recognized by syndromic features leading to a positive diagnosis, and that they are a high risk for surgery, but easily managed with anticoagulants.

This presentation started with the premise that hypercoagulable states and disorders are common but also commonly overlooked. Analyzed above are the historical reasons why hypercoagulability, recognized as clinical entities only since circa 1990, has been "late to the party" of medical knowledge and teaching. Why though are these disorders common? It is because coagulation is a complex N-body non-linear multi-control system. That it works so well at all is a miracle of natural engineering. However, with so many interacting elements and levels of feedback and control, it is inevitable that things will get untuned or unbalanced when the system is perturbed by disease and injury. The healthy system has great capacity to respond to stress and keep centered the prime output, the conversion of fibrinogen by activated thrombin. However, extreme extrinsic stresses or loss of controllers through

intrinsic disease can exceed or overwhelm the system's capacity to right itself. Physicians are universally familiar with what happens when the system is unbalanced toward hypocoagulability and bleeding, effects that are usually overt and often immediately life threatening. In contrast, hypercoagulable consequences are often subtle, chronic, and easily mistaken for other disorders. Thus, through a conspiracy of medical history and the physics of complex systems, these prevalent disorders remain "off the radar screen", their complications usually attributed to some other pro forma diagnosis. Once you are cognizant of these disorders and begin to recognize them by thorough history, physical exam, and laboratory evaluation, they will no longer seem arcane, occult, or uncommon.

Hypercoagulability. Hypercoagulable disorders are a modern discovery and concept. They are common, but all too often under-appreciated, unrecognized, and overlooked.

Positive Diagnosis. Hypercoagulable disorders and ulcers can be diagnosed on specific criteria. They are NOT diagnoses of exclusion. In taking a 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. This tetrad-pentad (4 point personal history, plus family history) can be your guide to taking a history and assessing risk. **(1)** Thrombotic or embolic event. **(2)** Autoimmune cvd-ctd. **(3)** Wound pathergy or ulcer. **(4)** Miscarriage. **(5)** Family history of same.

Pathophysiology & Triggers. The coagulation system is a complex multi-control system, dynamics governed by principles of non-linear dynamics. This means that affected patients are not always in a hypercoagulable state. When hypercoagulable dynamics start, they can "lock in" to a persistent state. Be cognizant of the interplay of coagulation and inflammation, and of Virchow's Triad (state of the vessels, state of the flow, inherent coagulability of the blood). Do what you can to treat or minimize those collateral conditions which tend to trigger thrombotic events.

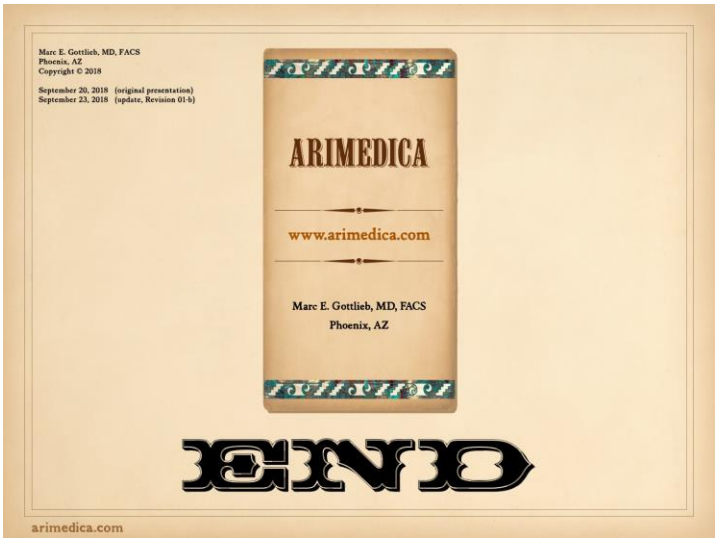
Wounds, Trauma, & Surgery. Hypercoagulable patients & states are prone to wound pathergy and infarction. In face of odd, unexpected, repetitive wound complications, suspect hypercoagulability. These are prime situations for principle of "do not do too much, too soon, too often".

Anticoagulation. Anticoagulation is the 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. Anticoagulant therapy restores normal wound healing.

Comprehensive Treatment. Treatment must be for acute complications and for the chronic primary disorder. **(1)** Treat acute events to stop progression, restore flow, limit infarction. **(2)** Anticoagulation, treat related disease (e.g. steroids), avoid extra injury, wound care. **(3)** For wounds, anticoagulation is necessary, and may be sufficient to heal by natural contraction or to permit basic surgery. For the most refractory, pathergy prone, at-risk wounds, consistent good results come from the triad: ***anticoagulation*** (arrests pathology), ***hbo*** (permits revascularization to restore physiological deficits), ***regenerative biomatrices*** (surgery without wound pathergy).

Managing Surgery. Start anticoagulation as soon as possible, pre-op when possible (and steroids as needed). Run anticoagulants during surgery. Continue anticoagulants until wounds heal, then 3 - 6 months (or longer) as the wounds mature.

The illustration depicts leeching in the 17th century. Despite the irrational uses of the little critters back then, today they have found legitimate use for two reasons. One is to provide venous outflow in struggling flaps and replants. The other is as a source of hirudin, a natural anticoagulant that has found its way into modern pharmaceutical practice. The engraving is from ***Historia medica, in qua libris IV, Animalium natura, et eorum medical utilitas exacte & luculenter tractantur*** *(History of medicine in four books, Nature of animals, and their medical uses exactly and clearly treated) published 1639, author* ***Guillaume van de Bossche*** *(born c1600), a physician and naturalist from Lièges, Belgium. Woodcuts are by Flemish engraver Christoffel Jegher (1596-1652), a collaborator of famous Baroque painter Peter Paul Rubens (1577-1640).*



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