PRINCIPLES OF SURGERY – WOUND PATHERGY (WHEN NOT TO OPERATE)

SITUATIONS TO AVOID THAT WILL CAUSE NECROSIS, DEHISCENCE, WOUND FAILURE, & RELATED COMPLICATIONS

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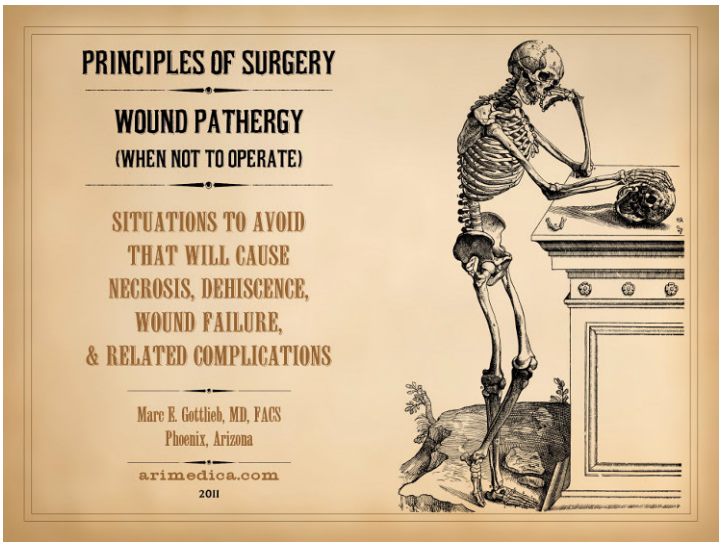

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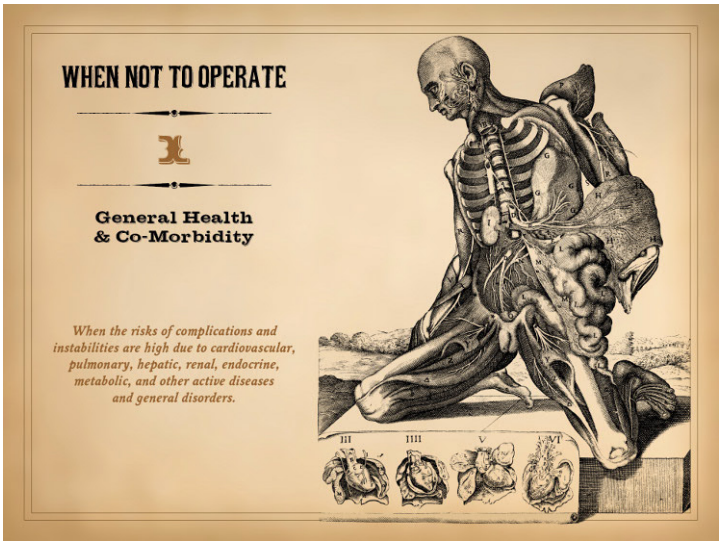
This presentation was developed 2011 - 2012. It addresses the important subject of wound pathergy, the emphasis being on how it can complicate surgery and jeopardize the patient via necrosis, dehiscence, and other forms of wound failure. In short, it is a talk about "when not to operate".

This illustration is taken from the works of Andreas Vesalius (1514-1564), native of Brussels, and eventually professor of anatomy at the prestigious medical school in Padua. His grand opus, De Humani Corporis Fabrica was first published in 1543. The book illustrates his anatomical dissections with many inspiring woodblock prints that are as exquisite in their artistic interpretation as they are in their scientific detail. The illustrations are exceedingly accurate, even by today's standards. This work established anatomy as a scientific discipline and ended a thousand years of stagnation in European medical knowledge. It is justly considered one of the great masterpieces of not just science and medicine, but also of the printer's craft (with all just accolades to printer Johannes Operinus) and even of human civilization itself. This image is especially important, because the skeleton is positioned such, with extremities flexed-extended and pronated-supinated, and with the accessory skull, hyoid, and ear ossicles displayed, that every single bone in the body can be seen in this one view. Nearly everyone who sees this image, contemplation of a skull upon a tomb, likens it to Hamlet's soliloquy upon Yorick, but Hamlet was not written until 1600. Nonetheless, the concept of contemplation is worthwhile to the study of wound pathergy, pausing to understand the risks of certain diseases and operations, taking time to formulate a safe and considered strategy for solving, without complications, the problem that your patient has.



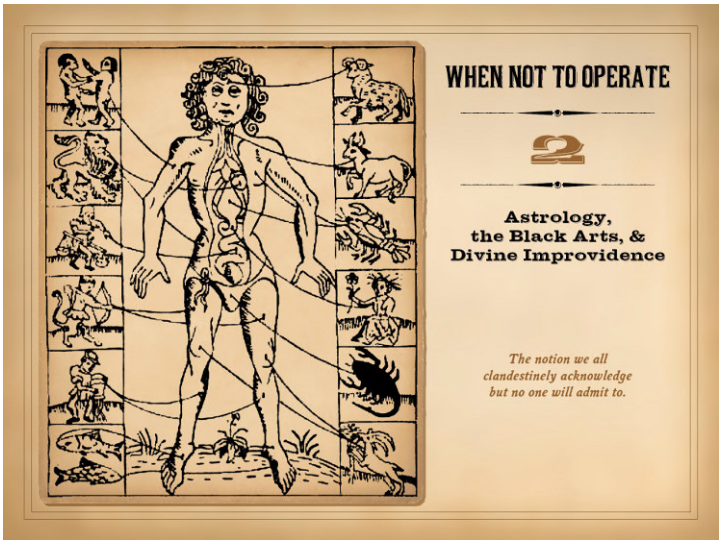
2

When not to operate – 1

General health & co-morbidity

There are a variety of reasons to delay, postpone, cancel, and otherwise opt not to do surgery, even when the nominal indications are met for a given disease, diagnosis, and clinical situation. One set of such situations is the general health of the patient and the presence of illness or co-morbidities which put the operation or the patient at risk. These include various cardiovascular, pulmonary, hepatic, renal, endocrine, metabolic, and other active diseases and general disorders. These circumstances and principles are familiar to all surgeons and physicians and need no further elaboration here.

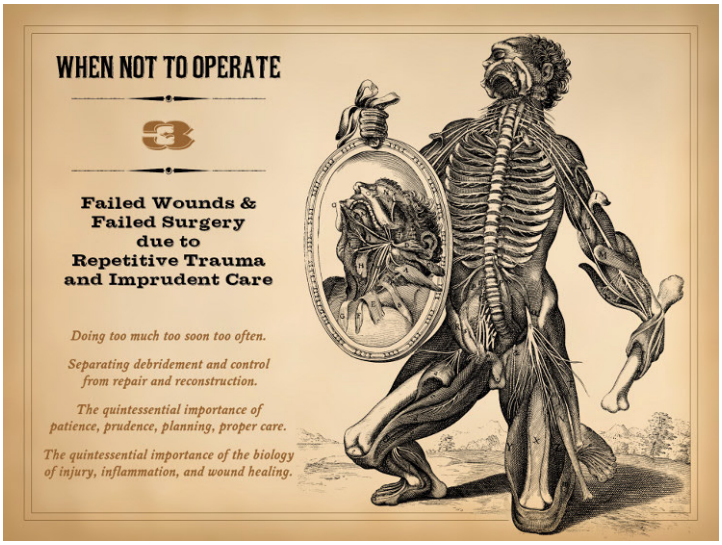
The illustration is by Pietro Berrettini (1596-1669). Known popularly by his city of birth, Pietro da Cortona was artist and architect of the highest preeminence, epitomizing the High Baroque in Italy, and perhaps second only to his contemporary Gian Lorenzo Bernini in influence and cultural significance of that era. Along with his geometrically detailed baroque architecture projects and his extravagantly dramatic paintings and frescoes, he created one of the more interesting and beautiful bodies of work from this era, the Tabulæ Anatomicæ. The work is a mystery – no one knows why he did them, who commissioned them, under what circumstances he had the wherewithal to make them, nor even when exactly they were made, the best estimates being 1618, before he earned his fame and came to the attention of patrons and commissioners. They were published posthumously in 1741 , 72 years after his death, over a century after they were drawn. The circumstances of their rediscovery and impetus to publish them is not fully understood. In any work of this sort, the artist needs crucial collaborators, in this case the woodblock engraver being most likely Luca Ciamberlano, and his anatomist being probably surgeon Nicolas Larchée. Shown here is Tabula IX, demonstrating the internal viscera. Like all of the Tabulæ Anatomicæ, it has a sense of artistic pose and drama that few anatomical studies have, eminently Baroque and eminently da Cortona. It is included here to remind of the significance of internal diseases, and why they must be under control before non-emergent surgery is done.



3
When not to operate – 2
Astrology, the black arts, & divine improvidence

A second set of reasons not to operate is the misalignment of the stars. No, I do not subscribe to any principles nor belief in Astrology, the Black Arts, nor other forms of paranormal and metaphysical study. However, I suspect that nearly every surgeon has felt at times that his horoscope was against him or that the Evil Eye was upon him. We have all, I believe, experienced times when we and our patients have had a run of good luck, so much so that the axe must soon fall, and then we go through a week or two when nothing quite seems to go right. Call it Divine Improvidence or whatever you wish. Sure, this slide is a joke, but it is nonetheless a notion we all jokingly or else clandestinely acknowledge, even if we do not admit or seriously believe it. Perhaps one of the best investments any hospital could make is to hire a staff astrologer, someone with unfettered authority to shut the OR down whenever Karma and the planets are out of kilter – there are surely many more foolish and irrelevant things that hospitals waste their money on already.

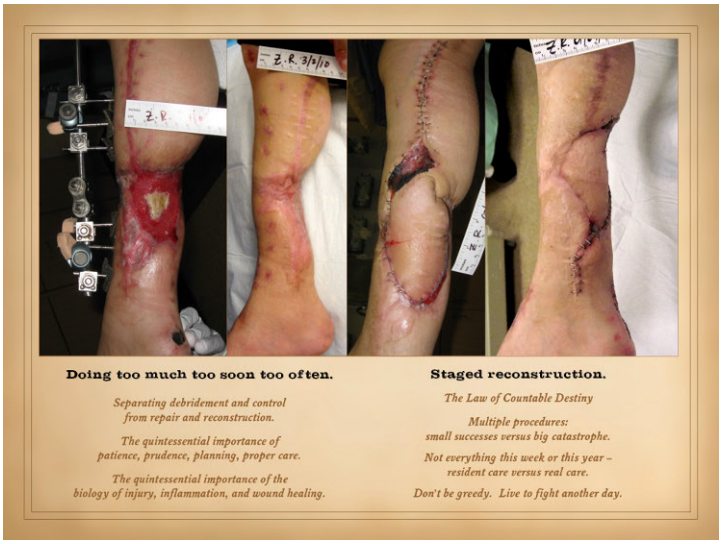
The "Zodiac man" was (and still is) a common figure in books that purport to equate our bodies and our health to the constellations and metaphysical influences. Such charts appeared in the arts and writings of various cultures around the world at various times in history. In Europe and Western civilization, these ideas were au courant philosophy and sanctioned knowledge in the Ages of Faith, spilling over well past the Renaissance, and relegated to alternative non-academic status only by the Enlightenment and Age of Reason in the 18th century. This illustration was found on an internet source, referenced only as "from a woodcut in a 1702 almanac; probably reproduces an earlier image". The artistic style suggests that the original was probably from a German book somewhere around 1500-1550.



4
When not to operate – 3
Failed wounds & failed surgery due to repetitive trauma

The third reason not to do surgery is all too serious, and it is an important and necessary lead-in to the main subject of the fourth reason not do surgery. The issue is failed wounds and failed surgery due to repetitive trauma and imprudent care. Simply put, it is what happens to wounds subjected to too much or repetitive trauma, what happens when a surgeon does too much too soon too often. In reading through the next several slides, keep the following principles in mind: **(1)** the importance of simply not doing to much too soon too often, because wounds will fall into a state of persistent injury and inflammation that will prevent healing; **(2)** the importance of separating debridement and control from repair and reconstruction (separate procedures at separate times); **(3)** the quintessential importance of patience, prudence, planning, and proper care, the virtues necessary to restore complicated and pathological wounds back to health; **(4)** the quintessential importance of the biology of injury, inflammation, and wound healing, the relevant sciences that explain why these wounds are at risk and why these principles must be adhered to.

This illustration is also from Pietro da Cortona, Tabula XII, showing the spinal and some of the peripheral and cranial nerves. There is a certain pathos to this image, serving as a way-post to those who might forget that a surgeon must not do too much too soon too often nor be tempted to do otherwise, else his patient will pay the wages of that indiscretion.



5
Patience, prudence, planning, proper care

Most surgery can be categorized in one of two ways, death and disease (saving lives and curing illness) versus repair and reconstruction. Most doctoring and medical education seem to get focused on the acute disease issues rather than the long term restorative issues. This is understandable, because in Surgery, many of the miraculous cures that we accomplish are dramatic single interventions for high profile problems – cut out the cancer, reduce and fixate the fracture, relieve the bowel obstruction, evacuate the intracranial hematoma, revascularize the thrombosed extremity, etc. The downside of this is that there is a mentality about surgery that any nominally "surgical" problem can be fixed with an operation, and that if the first operation fails, then the problem can be fixed with another operation. However, there are situations in which surgery cannot succeed. If the causes of wound failure are not corrected, then the factors that impaired the first operation will simply impair the subsequent operations, and each time the adversity gets worse, in the form of increasing inflammation, thrombosis, edema, etc.

There is a flip side to this discussion though, the necessity of multiple operations as part of a staged reconstruction – and much of good reconstructive surgery is done in incremental small stages, making sure that each one is successful. What is the difference then between doing too many operations, the bad, versus doing so many operations, the good? This can be explained by first looking at a case study. Illustrated is an 18 year old woman injured in a car accident. The right leg had an open comminuted tibia-fibula fracture with loss of 6 cm of bone length and loss of most of the soft tissues posterior to the fracture. The patient was advised to have an amputation, but she rightly refused. Not only was amputation unnecessary for something that can easily be restored, but she also had significant upper extremity injuries which would make the use of crutches, walker, and prosthesis difficult. The key components of her tentative reconstruction are to restore length to the tibia, reconstruct the posterior tibial nerve, and maintain ankle posture, mobility, and gait.

Left, the leg in an external fixator, wound still open, on first consultation 3 months after the original injury. ***Second***, the leg at 9 months, completely healed and tibia stable after using a regenerative collagen-gag matrix (Integra®) to restore skin over the fracture. Now that the leg has been repaired and acute phase injury and wounds are subsided, the latter phase reconstruction and restoration can begin. ***Third***, the leg at 10 months, part way into a restoration of skin and fascia over back of the leg. This was mandatory as a prelude to later visceral reconstruction (tibial nerve grafts, achilles tenolysis and reconstruction, tibial and limb lengthening). This restoration was done with a large random flap taken from the upper half of the leg, the flap being inset after a single preliminary delay, and then the base of the flap divided and inset a few weeks later. ***Right***, at 18 months, this is the leg a few days after the tibial nerve reconstruction, showing the incisions where the flap was lifted to place the nerve grafts (3 strands, each 10 cm long, taken from the contralateral sural nerve). This is the current status of the patient. Once this is healed and there are signs that most axons have crossed the proximal coaptation, then the next (perhaps last) major procedure will be to place a limb lengthening frame (including tibial osteotomy and achilles release). The bone distraction or transport process will itself then take 2 - 3 months. Each and every of these procedures was completely successful, healing and achieving the desired result without morbidity, disability, or complication, mostly as an outpatient with just a few days net in the hospital. The estimated total time to complete her reconstruction will be about 2 years, perhaps a bit daunting for any patient looking ahead at the process, but ultimately forgotten when life and its functions start to return to normal thanks to the good results. The 2 years invested here on a good reconstruction will more than pay for itself over the next 60 years (or whatever) of a sound functional life, especially since the investment cost little in the way of risk and time distracted from real life.

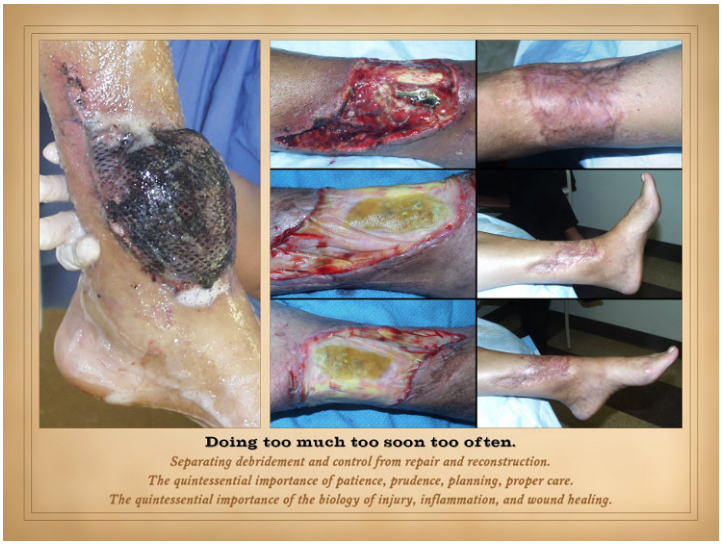
What is it about a successful staged reconstruction that allows it to heal and do well with multiple procedures? Why was a staged reconstruction necessary, why not just do it all in one grand operation? The keys to success here were that each procedure focused on just the one or two items that could be accomplished safely under the circumstances of the moment, avoiding doing things where the requirements of splints and stability would compete with needs of movement and mobilization, making sure that flaps would survive using the standard strategies of good "flapology", restoring "essential coverage" soft tissues before attempting reconstruction of visceral parts – all standard stuff in the realm of reconstructive surgery. Most importantly – reiterate most importantly – other than the flap delay which has its own physiological time frame, the various stages were done several months apart, enough time between each to permit the resolution of edema and some maturation of scar.

We can here enunciate a crucial law that governs good reconstructive surgery, what I now author as the "Law of Countable Destiny". It simply states that for many of these reconstructive situations, that each patient is destined to have X number of operations. The surgeon can decide how he wants to spend his allotment. He can do one heroic glorious big operation then spend many smaller operations cleaning up the resulting mess, or he can do small incremental procedures, each a complete success in its own right, each contributing to an overall grand result that was planned from the beginning. It is certainly true that if a reconstruction can be accomplished predictably well in one operation, then that is what should be done, and there are indeed many opportunities to do so, but for many reconstructions, multiple small procedures is the spirit and salvation of a great result.

There is an inherent bias built into our system of medical and surgical education that favors short term acute management and the immediate result. High acuity high drama events, such as trauma and peritonitis and sudden vascular problems generally need immediate one time operations to stabilize. Surgical residents are all too easily focused on the glamor and excitement of these events. However, there are also many low acuity and elective problems, all equally important, but managed through surgeon's offices and outpatient facilities. These are often sequestered from a resident's experience or interests. Residents have only a 2 or 3 month "rotation" perspective on their patients and

problems, even when the relevant care will take 2 or 3 years, so young surgeons tend to come away from their training with the idea of "get it done now, get it done all the way". That attitude simply does not work for good reconstructive surgery. When in doubt, don't be greedy, do less and "live to fight another day". Small successes versus big catastrophe is always the preferable position.

Notice the relationship of this patient's management to the principles enumerated on the last slide: **(1)** *Doing too much too soon too often.* Yes, surgery was done often, but never too much, and never too soon. **(2)** *Separating debridement and control from repair and reconstruction.* Wounds were allowed or made to heal, then time was allowed for resolution of inflammation and maturation of scar before undertaking any or further reconstructive procedures. **(3)** *The quintessential importance of patience, prudence, planning, proper care.* Patience, prudence, and planning were built into the process from the beginning – from the overall strategy and sequential design of the reconstruction, through not getting greedy and doing too much at any single procedure, and being patient enough to wait the requisite time between procedures. **(4)** *The quintessential importance of the biology of injury, inflammation, and wound healing.* The reasons for these all important principles reside in the basic biology of injury, inflammation, and wound healing. These are the local laws of the surgical universe, and successful reconstruction depends on working within the law.



6
Too much too soon too often

In comparison to the last case, consider this one. A 50 year old woman had a closed tibia-fibula fracture, treated by plate-and-screw fixation through a midline anterior ankle incision. Several weeks after the original events, she developed some drainage from the incision. There were no gross inflammatory changes, nor any pain, ulceration, or skin changes other than the small sinus that developed to allow for the drainage. Two prudent strategies could have been followed to resolve this. **(1)** Antibiotics along with topical wound care and compression for edema control could have been tried safely for 4 – 8 weeks. It might not have worked, but it would have been entirely safe, risking no collateral damage, burning no bridges. **(2)** Either preemptively from the beginning, or else if plan #1 failed, then the hardware could have been removed, the ankle placed in a cast or cast brace or external fixator, and then in a few weeks after antibiotic therapy it could be stabilized with an endosteal nail or even just bone grafts and a cast. This too would be circumspect, safe, and risk little and burn no bridges.

If all else failed, if the fracture became abscessed, then aggressive debridement and late bone reconstruction could be done. That would have been proper from the beginning if the patient had any evidence of significant bone or soft tissue deficits or acute or early inflammatory or suppurative complications, but that was not the situation here in this case of a low impact ground level fall. The problem with an overly ambitious operation when not indicated is that you risk making the problem worse, creating new wounds and defects, more inflammation and ulceration. If the prudent safe strategies fail, then all you have lost is time and dashed anticipation – you can still get a good result, and the indications for the more aggressive procedure will have been confirmed. If the overly ambitious care fails, then the risks are for prolonged morbidity, disability, prolonged care, and possibly even amputation.

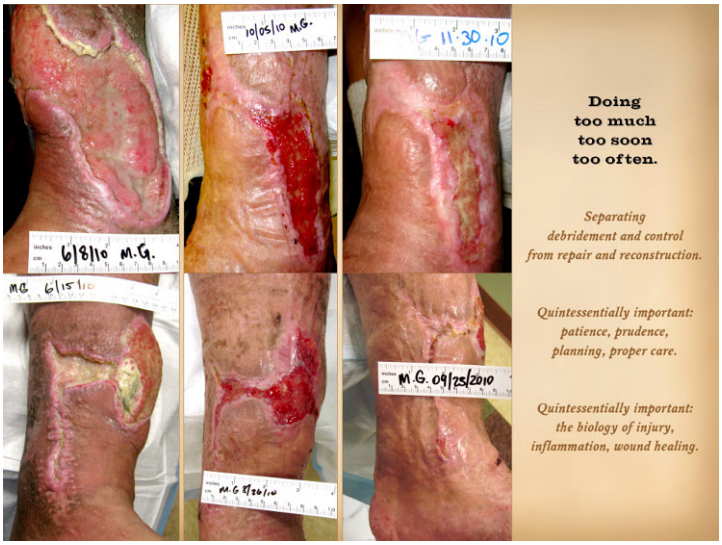
In this case, the surgeon excised healthy skin to make way for new flaps. When local flaps or closure failed, the patient had a rectus abdominis free flap, and when that thrombosed and failed, she then had a latissimus free flap. When I was asked to see the patient, the second free flap was dead, ***left***. There was pus underneath, thrombus in the vessels, and generalized edema and erythema throughout the area. This is a perfect example of doing too much too soon too often. Repetitive surgery and injury makes more thrombosis and inflammation. Thrombosis, inflammation, edema, and suppuration ensure that subsequent procedures will have complications or fail. Even the act of trying to close or cover a "pus wound" is a violation of at least 12 or 15 of the 10 commandments of surgery. The entire affair was foolish and unnecessary, incurring great time and monetary expense, incidental morbidity, and loss of major anatomical structures, all for naught – not just neutral, not just zero sum, but a significant deficit and detriment to the patient – all avoidable.

At this point in her care, the imperative is for simple safe activities that are sure to eradicate bioburden, quench inflammation, eliminate edema, allow heightened thrombogenicity to subside, and otherwise return the wound and tissues to a state of quiet non-acuity. At this point, the fracture and hardware are there, and they will need a later solution for salvage and healing, but not until this has all be rendered healthy and quiet. Resolution began with a complete debridement, then perfunctory basic care with good wound hygiene, appropriate topicals (silver sulfadiazine), and edema control. This care will keep any fracture and hardware just as clean and healthy as the wound in general, and the hardware can continue to do its job providing fracture stability. When all acute and pathological issues were resolved a few weeks later, then a strategy for closing the wound and healing the fracture could be implemented.

In this situation, customary plastic surgery procedures for closing the wound were no longer an option, with no remaining local flaps and many prohibitions against trying another free flap. Instead, when the wound was suitably clean, closure was done using a regenerative biological matrix as a skin substitute over the fracture and hardware (Integra collagen-gag matrix). Its initial placement served as a high grade artificial skin. Whenever the silicone "epidermis" of the material was near its time to come off (typically at 3 – 4 weeks after the matrix has generated a living neodermis), a fresh piece of new Integra was placed to maintain coverage with a biologically compatible artificial skin. This plan was not meant to completely close the wound or be the final fix. Instead, the initial intent was to continue the strategy of cyclical matrix replacement until the fracture was healed. After that, the plate would be removed and skin restored with simple skin grafts, probably in 3 or 4 months. However, the

matrix allows for tangential histoconduction, and that is what happened, the neodermis creeping in from the edges growing over the plate. After the third piece of Integra, a complete competent lamina of new living tissue covered the plate, and the regenerated neo-dermis could then be skin grafted. The reconstructive sequence is shown in the ***center column***. The healed skin including a healed fracture and normal ankle motion are shown in the ***right column***. There were no complications nor setbacks of any kind. The patient became quite skilled with the required care, permitting her to take an out-of-country holiday vacation for three weeks while the third Integra was in place. It has remained healed for nearly 10 years, the hardware uncomplicated and still in place, a wonderful result that incurred no morbidity nor risk to the patient.

Consider this patient's management in relationship to the 4 principles we have enumerated: **(1)** *Doing too much too soon too often.* In the early acute, morbid, complicated phase of her care, surgery was done too much, too soon, too often, and everything went wrong. In the latter phase of her care, surgery was done often, but in small specific safe increments at appropriate intervals geared to the biological realities and time constants within the system, and the result was even better than expected. **(2)** *Separating debridement and control from repair and reconstruction.* The complicated mess and mayhem of the early phase was debrided and good wound care was initiated, and then the wound was allowed time to subside before undertaking any further closure. When the reconstructive activities were then started at the proper time, everything went well and healed. **(3)** *The quintessential importance of patience, prudence, planning, proper care.* In the early phase of her care, each failed activity was an unplanned ad hoc reaction to unexpected or undesired events. "Unexpected" however is a misnomer, because although the first surgeon did not expect such trouble, that trouble was indeed predictable, and the purpose of this presentation is to raise awareness of such adverse expectations under predisposing conditions. In the latter phase of her care, patience, prudence, and planning were built into the process from the beginning, and they were rewarded with a result that exceeded expectations, obviating the planned final procedure of plate removal and skin grafts. **(4)** *The quintessential importance of the biology of injury, inflammation, and wound healing.* To reiterate the mantra stated on the preceding slide, the basis for these all important principles is in the basic biology of injury, inflammation, and wound healing. These are the laws of the surgical universe, and successful reconstruction depends on working within the law.

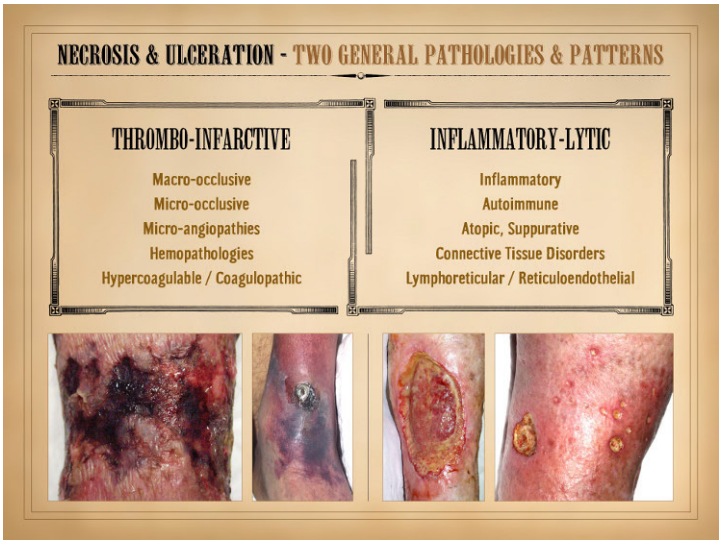


7
Too much too soon too often

Not to belabor a point . . . but we must . . . we must! Too much too soon too often, this is the demon of failed surgery. This case study illustrates the point even more dramatically than the others, because the key to this patient's recovery was simply to stop doing surgery. This is a 66 year old man with a complex fracture of the left ankle including overlying skin injury. His fracture was reduced and fixated with hardware, and the bone itself healed and remained inherently uncomplicated. Initial soft tissue surgery to cover the fracture and hardware succeeded in protecting and healing those essential elements. However, the wounds remained open at the skin level, and rather than wait and be prudent and deal with benign missing skin in its own due time, instead the patient was taken on an obsessive quest and holy crusade to get that damned missing skin in place. One after another of various flaps, grafts, and debridements and closures failed. The patient had 15 operations under anesthesia in just 18 days. Eighteen days, fifteen anesthetics, fifteen failed procedures. Not surprisingly, with each event, edema, inflammation, and skin and wound infarcts got worse. If wound closure surgery fails the first time, a second try is fair after proper preparation. A third try might be justified in select cases with compelling reasons. After that, the chances of successfully closing a problem wound over short intervals is essentially impossible. When he was seen for first consultation, there was intense inflammation , edema, and drainage throughout the wound and periwound, indeed the whole leg and ankle. Topical care had not been rendered or was non-specific and ineffective. There had been no compression nor other edema control modalities. In short, through 15 cut-and-sew procedures, nothing had been done to treat or improve the key pathophysiological stresses, mediators, and instigators of the perpetuated inflammatory state.

In any case of wound pathergy and multiple failed procedures, it is necessary to do a review of systems, take an inventory of relevant history and features, and get laboratory studies if needed to rule out an underlying disorder of the varieties to be discussed in this presentation. In this case, there were no indicators of autoimmune or hematological or coagulopathic or vascular diseases. The photo series starts on the ***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 panel*** shows the progress after several weeks of the same care. Some skin grafts to expedite closure would have been valid at this point, but the patient, seeing the progress, was opposed to any further procedures. The ***right panel*** shows the medial and anterior aspects of the wound healed, with a remaining open area slower to heal, as expected, over the lateral margin of the fibula.

In this case, there was nothing wrong with the patient other than too much surgery, too often, too soon, 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 the simple treatments that correct the adverse pathophysiologies that prevent healing that get stirred up by surgery. 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 disorders of inflammation, immunity, thrombosis, circulation and related factors which cause, sustain, and perpetuate these adverse events? When a surgeon follows the rules and does not violate any of these principles, yet the wound or flaps or surgery undergo necrosis and ulceration, why? What caused these unexpected adverse events, what are the risks for more trouble, and how can problems be corrected or circumvented?



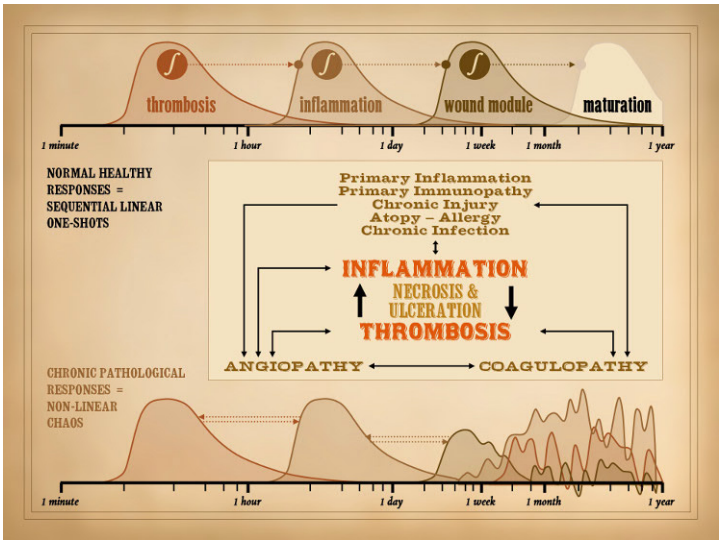
The biology of injury, inflammation, wound healing

In order to understand wound pathergy and unexpected wound and tissue complications, it is first necessary to understand the underlying pathology of necrosis and ulceration. "Necrosis" and "ulceration" are the two main words that describe the active onset and evolution of a pathological wound. As will be discussed throughout this presentation, there is quite a large spectrum of diseases which can cause necrosis and ulceration. Regardless of the specific primary disease or associated risk factors, the first major concept to understand is that there are two patterns and final pathways to necrosis and ulceration – the thrombo-infarctive pattern and the inflammatory-lytic pattern. These patterns, evident, indeed usually obvious on clinical exam, reflect specific and interrelated pathophysiological events which destroy tissue.

(1) Thrombo-infarctive necrosis and ulceration are 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 and CAP wounds (Chronic And Pathological), thrombo-infarctive pathologies typically cause 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, absence of edema, and absence of gross inflammatory changes. Laboratory measures of perfusion, such as $TcpO_2$, laser doppler, and multi-spectral imaging are likely to show flow 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 chemistry. Clinically, these are ulcers 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. Many CAP ulcers have features that are obviously of one origin or the other, predominantly thrombo-occlusive versus inflammatory-lytic, and thus they can easily be discriminated, by simple physical exam, as to which underlying pathology predominates. However, because of the intimate and intricate inter-dependence of inflammation and thrombosis, many ulcers will have features of both patterns.

There is a third major pattern or cause of tissue loss or destruction – trauma. This 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). As will be explained further in later slides, angiocytes and fibroblasts, the two constituent cells of the generic stroma and wound healing process, 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.



9
The biology of injury, inflammation, wound healing

Necrosis and ulceration can occur acutely, such as devascularization of tissue from trauma or else a large occlusive thrombus in an atheromatous femoral or coronary artery. Principles of management for these conditions are well defined, and the response to treatment is generally predictable and usually successful. When necrosis and ulceration occur without anticipation, or if they plague what should have been an ordinary injury or perfunctory operation, then something else is at work. Thrombo-infarctive and inflammatory-lytic processes are the root of these events. Sometimes the pattern of injury is predominantly or almost exclusively one or the other, but more often a wound will have features of both. The association between these two domains of pathology, thrombosis-infarction and inflammation-lysis, is a crucial one. Their interaction and mutual dependence sits at the center of the adverse states of necrosis and ulceration. The abnormal sustentation or perpetuation of necrosis, ulceration, and wound failure depends entirely on abnormal or heightened or pathological interactions between these events.

Repetitive injury, thrombosis, inflammation, necrosis, and ulceration are at the core of wound pathergy and wound failure. This particular presentation is more of a clinical rather than scientific presentation. It focuses on the underlying or a priori primary illnesses and comorbidities which can lead to these adverse states. The emphasis is on clinical recognition and care, not on the biological minutiae that explain the pathways to wound infarction and lysis. However, such scientific details are crucial to understanding the adverse clinical states. This particular slide therefore presents a glimpse at the dynamical pathophysiology that leads to wound pathergy when thrombo-infarctive and inflammatory-lytic events become amplified and perpetuated. It is an abridged version of a subject presented in detail in a set of studies and papers first presented in 2009 and 2010. These papers and supplementary materials are all available at **www.arimedica.com** . See **Slide 11** for the links. The following text is a brief explanation of these concepts.

The normal healthy response to injury is composed of several dynamical domains or events: recognition of the injury (thrombosis, etc.), then reaction to the injury (inflammation), then repair of the injury (wound healing). The dynamical behavior of each of these events and of the integrated process can be described as convergent one-shots. Each of these events is triggered into action by some sort of acute or threshold stimulus, then each runs its course doing its appointed tasks, then each extinguishes or dissipates itself as its job is accomplished, the system converging on a healed wound or restored tissue. The term “one-shot” comes from electronics, jargon for a “monostable vibrator”, a circuit which can switch state (off-on, negative-positive, low-high) when triggered, and then it returns to stable baseline after discharge through an R-C circuit, now in standby again awaiting another trigger. This is the basis for most timing circuits. The time-dependent nature of the triggered electronic event and the resulting output waveform is completely analogous to the phases of injury-response.

The **upper panel** illustrates four cusps of this dynamical process spaced out along a logarithmic timescale (including the late term event of wound maturation which is of no consequence to the acute phase issues emphasized in this presentation). This is a dynamical picture of the normal response to injury and the normal process of wound healing in the normal healthy unimpaired wound. Each of the constituent responses has one-shot dynamics, the integrated process is a linear series of one-shots, and the aggregate response is a one-shot. The disordered dynamics of the sick wound begin when these orderly convergent one-shots are disturbed, either by extrinsic stresses on the system or by illness within the system.

The cusps shown are idealized abstractions, non-rigorous conceptualizations of the wound and its dynamics. Each of these “black box” events of thrombosis, inflammation, and wound repair houses a complex control system which regulates the response and output of its respective system. For example, as the “wound module” curve goes high and then low, it represents the load and output of the wound repair cells as driven by the wound control loop, ramping up as they become activated, then decaying back to standby as they wrap up business as the wound closes. This conceptual kinetic curve or curve-of-state is repeated for each of the main events: thrombosis, inflammation, wound module, and maturation. All of these events are coordinated with each other, but each is its own control system, each turning on properly for an appropriate trigger, and each “knowing” how to turn off when its business is concluded. Consider the roles and dynamics of each of these major events in the response to injury:

Injury: Consider what happens when a one-time incidental self-limited injury occurs – a cut finger, a surgical incision, a ruptured tendon, whatever. It occurs in the time frame of seconds-to-minutes, and then it is over. It too will have the same general shape as the other curves shown, and it could / should be added to the diagram as another hump on the left side, the “injury” cusp. The effect of the injury is to trigger thrombosis. The injury was brief, and by the time that thrombosis is getting underway, the injury itself is over.

Thrombosis: The term “thrombosis” is used here in a loose sense to refer to the aggregate injury recognition events that are based on a variety of blood borne elements – mainly plasma proteins, platelets, and leukocytes. Thrombosis can be considered as the on-off switch which recognizes injury and gets the rest of the process going. Remember, the thrombosis cusp as drawn here is a “black box” hiding a very complex machine that knows when to turn on, how to run its business, then how to turn on the next event and then turn itself off. When “thrombosis” is triggered, there are two factors which cause thrombosis to “rise” or ramp up: (1) the more potent and the more sustained the injury or trigger is (the integral of the trigger with respect to time), then the more potent is the net response; (2) thrombosis is also an auto-amplifying event which raises its own kinetics. Thrombosis will eventually reach a peak, and then start to decay. If injury was a one-time limited event, a one-shot, then

there is nothing further to trigger thrombosis beyond the initial event. Thus, thrombosis gets its one-shot trigger, then it runs its course, and then it decays and extinguishes. Aside from its immediate effect to staunch bleeding, thrombosis has a crucial dynamical effect – it feeds forward into the control loop by triggering inflammation. Thrombosis builds then decays in the time frame of minutes-to-hours. In so doing, it acts as an integrator to build sufficient cell and chemical concentrations that at threshold trigger inflammation. By the time that inflammation is building, acute thrombosis events have largely subsided (there will still be old fibrin thrombi and platelet plugs in the field, but no new platelet aggregation, fibrin catalysis, or clot formation is occurring).

Inflammation: Inflammation is the next downstream event after thrombosis, and it is in turn the trigger for subsequent wound repair. Inflammation is turned on by the integrator effect of thrombosis. Thrombosis events build or accumulate the stimuli needed to trigger inflammation, and once inflammation begins, it is then self-running, even as the thrombosis events wane. Just like thrombosis, the inflammation cusp is a black box hiding a very complex multicontrol system. It too is self-amplifying, so between the thrombosis trigger and then its own dynamics, it builds to a peak effect. Assuming that injury and thrombosis were one-time one-shot events, then there is no further provocation for inflammation, and inflammation events will soon enough start to decay and wane. Aside from its important short term effects to defend the host and clean up the injury, inflammation also has the crucial dynamical effect of a feed-forward integrator to turn on wound healing. It does this by spawning and accumulating macrophages which are the controller for the wound healing control system. In the same way that thrombosis triggers inflammation, inflammation triggers healing as the controller builds to threshold levels, reaching a point at which macrophage and wound healing dynamics can be self-sustaining even as inflammation subsides. Inflammation events build then decay in the time frame of hours-to-days. By the time that the macrophage population is built and wound healing output begins, acute inflammation events have largely subsided.

Repair: Note the dynamical similarities between the injury-thrombosis-inflammation cusps, and the analogous transitions from one phase to another. That trend now continues in the jump or transition from inflammation to the repair phase, the proliferative wound module. As with the other cusps, the wound healing cusp is a black box housing a complex control system. Within the walls of the wound healing machinery, the wound healing control loop is always sensing variances between "normal" and "open wound", and it uses this error to drive the wound healing machinery. Once triggered, repair events will build to some peak of productive activity. As wound healing system output increases, the wound diminishes. This in turn lessens the error between open and normal, and the control loop is therefore less driven, and wound module kinetics start to wind down. Wound repair activity, the wound module, thus keeps pace with the demands of "open wound", ramping up then decaying as the process completes itself. This ramp up then decay is the same as for the preceding phases, but in a time frame of days-to-weeks. Wound module is also an integrator function that triggers another downstream one-shot event – maturation. Maturation begins only once the wound is epithelialized, meaning that maturation waxes only as wound module wanes.

Maturation: The integrated output of the wound healing cusp is a reconstituted stroma covered by epithelium which negates the condition of "open wound". However, it is not normal stroma, it is scar, a form of stroma that is excessively dense with vessels and connective matrix. This undergoes a process of remodeling or maturation that eventually restores it to proper architecture and density of the stromal structures. Maturation does not arise until proliferative wound healing events are waning as the wound approaches the state of "healed". Maturation is therefore a tangential or derivative event, and like everything else it is its own control system within its own black box domain. The scar is the integrated output of the wound module, but it is also the feed forward input into the maturation block and curve. As with the other major events, maturation rises to a peak dynamic then fades, with its time frame measured in weeks-to-months.

In the dynamics of the normal wound, in the progression of injury → thrombosis → inflammation → repair → maturation, there is a crucial additional relationship implicit in the diagram – the anatomical stratification and timewise separation of these events. Yes, these events are contingent, each downstream event being triggered by the preceding cusp. However, aside from a handshake and the flip of a switch to get things going, these events and phases, and their constituent cells and structures, actually have only limited contact with each other. This is in part because wound anatomy, the arrangement of its cells and structures, is not just an amorphous homogeneous bowl of pudding. It is highly structured, even within the few vertical microns or millimeters of its existence. The vertical anatomy of the wound is a timewise historical view of what has happened after injury, with the top happening now, and the strata underneath being progressively older. Thrombosis events are in the topmost layer. Inflammation is there and in the aminoglycan layer underneath, repair events are below that, and maturation occurs later. These events overlap to some extent, vertically and in time, but the overlap is comparable to the overlap of cusps in the sequential phase diagram shown here, with preceding events waning as latter phases appear. As long as these phase relationships are maintained, and as long as there is no new injury, then each event runs its course with one-shot dynamics, and the net dynamics of the wound runs a smooth course from injury to maturation. (For detailed information about these aspects of wound anatomy and physiology, refer to the links on **Slide 11**.)

In situations of wound failure and wound pathergy, the dynamics of failure arise in aberrations of the orderly dynamics just explained, and those aberrations are induced by the various diseases of blood and thrombosis and circulation and inflammation and immunity that are the featured villains of this presentation. Imagine a patient who has surgery or trauma that results in a skin flap that is sutured back in place. Imagine that this is a "bad leg" with severe occlusive atherosclerosis, and that the flap immediately turns purple and then dies and dries out over the next few days. That event is clinically undesirable, but it is completely understandable. Even the dynamics of this undesirable but understandable event will be orderly, simple and smooth, just like strictly healthy events. However, what happens if the leg has only moderate atherosclerosis, or even marginal atherosclerosis but there is also some sort of platelet problem or a hypercoagulopathy or the patient has lupus or multiple sclerosis? What if furthermore you took necessary precautions by giving rheological agents or anticoagulants or steroids, yet in spite of those precautions, unpredictably on the 5th day or 10th day after surgery the flap which looked healthy and viable before that suddenly turns colors. How do you account for the unpredictable event that defied prophylactic care? Such an event is also understandable, but not certain or predictable as to if or when. This is a situation in which known and understandable multiple risk factors are interoperating. The system is deterministic, it obeys understandable rules of biology. However, when complex multicontrol systems interoperate, the actual state or trajectory of the system cannot necessarily be calculated or predicted in advance. This type of dynamical behavior is known as chaos. "Chaos" in the mathematical sense does not mean the same thing as in normal vernacular speech. A full discussion is beyond the scope of this presentation, but more information can be obtained in standard textbooks and at the **arimedica.com** website (see Slide 11). What is crucial to understand here is that unpredictable behaviors in complex systems are normal. This slide gives just a bit of insight as to why the situations we are discussing create this uncertainty.

In the **lower panel**, we can start to see where chaotic dynamics come from. This diagram is also missing the acute injury cusp at the left. However, imagine it is there, and consider this scenario. A single injury occurs, putting the other events into action, each following the other, each having one-shot dynamics, and each conforming to the general shape of the cusps shown. Keeping an eye on the logarithmic timescale at the bottom, imagine that at 12 - 24 hours another injury event occurs. Within a few hours, the downslope of the inflammation cusp will suddenly have another rise. This will result in new uprises in the other downstream events. Each event curve will then seem a bit more complex, although obviously the new blips represent the superposition of the new curves on the originals. If more injury events were to occur, then more event curves or phase cusps would be added. Assuming that each injury event leads to an exact repeatable profile of downstream events, then the resulting composite activity curves would be the superposition of x-number of original events, and the curves might start to seem very erratic or complex. Understand the significance of the phrase "exact repeatable profile of events". This means that the system response adheres to a precise set of rules – i.e. it is strictly deterministic. Although the composite activity profiles might seem complex, they just represent the superposition of multiple copies of the same "waveform". If you knew the precise shape or dynamics of a single response curve, then the entire data stream could be "deconvoluted" (a mathematical method) to see all of the individual injury events and the time that they initiated. The point is that with repetitive injury or events, the composite data stream might seem very erratic or "non-functional" or "non-analytical" (unlike a simple equation or standard function), yet there is strict rhyme-and-reason to the data.

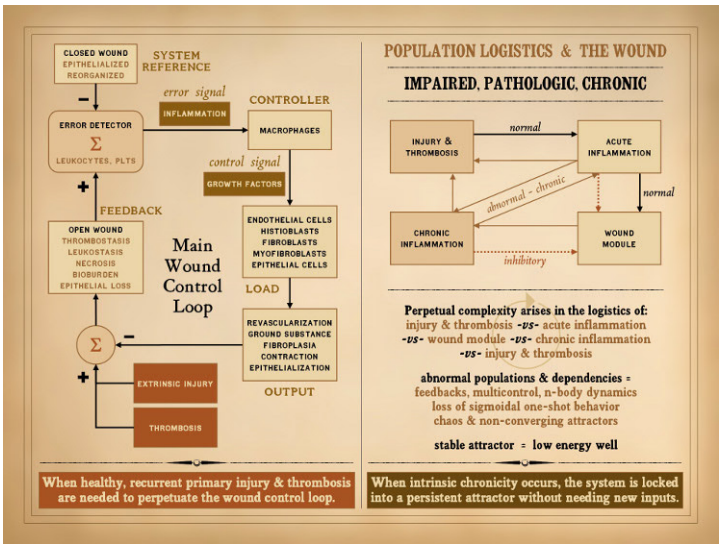
The situation in real wounds is even more complex, but the principles of deterministic rules and superposition of waveforms remain in force. In the lower panel, note the double arrows between the thrombosis, inflammation, and wound module cusps. In the normal healthy unstressed response to injury (the normal wound control loop), all of the dependencies between one control block and another feed forward, and the control loop runs clockwise. The net effect is the smooth one-shot convergent dynamics of normal healing. These double arrows, back and forth, imply a retrograde stimulus or feedback. How is that possible? When it occurs, it is abnormal, but it is possible and it does happen. "Abnormal" in the words of medicine is "pathology". These retrograde events are the consequence of sustained injury or diseased and disordered states of the wound. Consider first the inter-relationship between thrombosis and inflammation. Thrombosis triggers inflammation. From the point of view of conventional biology, thrombosis is explicitly how injury is recognized which then turns on inflammation. Dynamically, this is the normal feed-forward relationship of injury-recognition to injury-response, with one-shot thrombosis waning as one-shot inflammation is rising. However, inflammation can also cause thrombosis. Inflammation creates a variety of chemical mediators, mechanical-geometric-flow changes in vessels, changes in blood rheology, activation of leukocytes, and even further stasis and activation of platelets, all of which are potent thrombogens. The retrograde trigger of thrombosis by inflammation occurs under special circumstances, circumstances in which acute inflammation is sustained by some condition of continued injury or disease. When inflammation is sustained beyond its ideal one-shot profile, then it begins to act as an integrator or accumulator of those factors which risk triggering thrombosis.

Inflammation can also cause another "retrograde" dynamic – to create more injury. Inflammation is a destructive process. It is meant to be. Via leukocytes and a rich mix of proteases, inflammation lyses tissue. Lytic effects are normal, meant to destroy exogenous pathogens if present and to dissolve damaged stroma so that phagocytic and repair cells can perform their tasks. Normally, inflammatory lysis acts on the original injury and damaged tissue. By the time that wound module and repair are ramping up, inflammation is waning, and inflammation will not have destructive effects on the re-forming stroma. However, if some condition of repetitive injury, thrombosis, or other triggers of inflammation re-activate or even perpetuate acute inflammation, then inflammation will become fully active concurrent with active repair. Under those conditions, the destructive effects of inflammation not only suppress repair, but risk creating damage and destruction of restored or surrounding tissues, thereby causing progressive ulceration. Consider too that thrombosis can also have a retrograde effect to cause injury. Normally, thrombosis is a response to injury and damaged tissues. By the time that normal first-round inflammation and then repair are active, thrombosis is long gone, and it has no effect on subsequent new tissues. However, if some act of recurrent injury or sustained inflammation is present, enough to cause thrombosis when it should be gone, when things are trying to repair, then what happens? Thrombosis obstructs blood flow and causes infarcts. In chronic wounds, wound infarcts can and do occur. Small and multifocal, the aggregate effect can be quite damaging to the wound as a whole, undoing what has already been built, or causing progressive ulceration. Infarcted granulation tissue is a common observation in chronic wounds, such as coagulopathic and immunopathic wounds when there is a flareup of active disease. Next, note the wound module cusp on the lower panel. It never rises to full activity because of suppressive effects of sustained inflammation. These abnormal inter-phase dependencies can feed forward and be inhibitory as well as feed backward and be stimulatory. Finally, the lower panel also shows a backward arrow from repair to inflammation, another abnormal retrograde event that is not a normal property of healthy clockwise wound healing. This is the onset of chronic inflammation, the arrival of lymphocytes and plasmacytes in the proliferating wound module, a key marker of the chronic non-healing wound. They have an effect to disorganize repair, but also to provoke repetitive acute inflammation, a feed-backward effect which adds new events and superpositions of early activity which should ordinarily be long gone from the system during the repair phase.

The effect of new injury events, new thrombosis events, and all of these counterclockwise retrograde events is that if one occurs, then a preceding phase is bumped up to a new wave of response and reaction. This new bump then feeds forward, clockwise, sustaining overall wound dynamics. What should have been an up-and-down one-shot event then becomes disordered as the "waveforms" of each of these new rounds of activity are superimposed. The immediate response and dependency of one phase on another remains strictly deterministic, strictly driven by the physical, chemical, and biological rules of the system. However, by the time that enough of these aberrations have occurred, the waveform or data stream of sustained unsettled activity can seem anything but orderly. Instead of each phase or event rising and falling in sequence, eventually all events are simultaneously sustained and active. This is seen on the right side of the lower panel, where each event has a continued but erratic profile that continues without termination as long as the chronic wound persists. Indeed, this is the hallmark of the chronic wound, sustained and perpetuated chaotic dynamics that ensure repetitive reinjury and disorganization of the entire process such that the repair process can never get properly organized.

Non-healing and chronic wounds are characterized at the system level by the dynamics of chaos. You can see here what that really means to the wound, and why it happens. It happens when the orderly progression of wound phases and the orderly sequencing of control block dynamics as a set of single-cusp one-shots gets disordered. The disorder results from repetitive primary injury extrinsic to the wound, and from abnormal intrinsic feedbacks and retriggers. These abnormal or unanticipated events and dependencies have an effect to sustain the wound. This

sustentation can eventually reach a point where the repetitive or persistent interplay and recurrence of injury-thrombosis-inflammation can become a self-sustaining state that can no longer find a path to convergence. Since healthy wounds heal properly, what types of disease can induce a wound to get locked into a chaotic "attractor" of this sort? Keeping in mind the circular dependencies of thrombosis and inflammation, and the effects of both to create more injury, the diseases that induce chaotic wound dynamics are sustained conditions of primary injury, primary thrombosis, and primary inflammation. These include repetitive trauma, autoimmune states, atopy-allergy disorders, chronic infections, and hypercoagulable and micro-occlusive disorders of blood or blood vessels.



9b
The biology of injury, inflammation, wound healing

This slide is from other presentations, and it will not be fully described here. It is slide #26 from Part 3 of the series referenced on Slide 11. Refer to that for a complete description. This pane summarizes it with respect to the pathogenesis of long term wound failure, and to align the concepts of the chronic wound versus the subject here of when not to operate.

A healthy normally healing wound has two populations of cells, acute inflammation (blood borne leukocytes, i.e. neutrophils and macrophages) and wound module (proliferative local stromal cells, i.e. angiocytes and fibroblasts). Because the healthy wound wants to and knows how to heal, any recurrence or perpetuation of the wound reflects repeated primary injury and thrombosis. When intrinsic chronicity develops in a CAP wound (chronic and pathological), it is because a third population of cells has become resident in the wound, chronic inflammation, i.e. autoimmunity, with lymphocytes and plasmacytes. The 3-population wound becomes locked into a persistent chaotic attractor in which the altered and non-converging repair process no longer needs new extrinsic inputs to remain unsettled and non-convergent. It keeps reinjuring itself. This perpetual complexity arises in the circular logistics of: injury & thrombosis -vs- acute inflammation -vs- wound module -vs- chronic inflammation -vs- injury & thrombosis.

Left, the control loop of normal wound repair. This is the dynamical system level operation of a normal wound. Extrinsic injury and thrombosis are summed in (i.e. primary disease – trauma, allergy, immunity, hypercoagulability, etc). If the loop is running properly as a one-shot after an initial single injury, winding down as the wound heals, then adding additional such events expands the wound, causing more inflammation, and elevating the whole system to an earlier more active phase. Nonetheless, as a 2-population wound, when the new injurious triggers are eliminated, the loop runs its one-shot course, winds down, and the wound is healed.

Right, chronic inflammation has been added in with the other three major dynamical compartments (injury & thrombosis, acute inflammation, wound module). This adds a variety of new dependencies, both promotional and inhibitory, which complexify the patterns of feedback and thereby lead to chaotic behaviors. The 3-population wound is self-sustaining in a chaotic non-healing attractor. The wound does not heal until the third population abates, but the third population cannot abate until the wound is healed. This leads to chronic ulceration, non-healing, frustration in care, and the need for potent therapeutics to eliminate the third population or break the attractor.

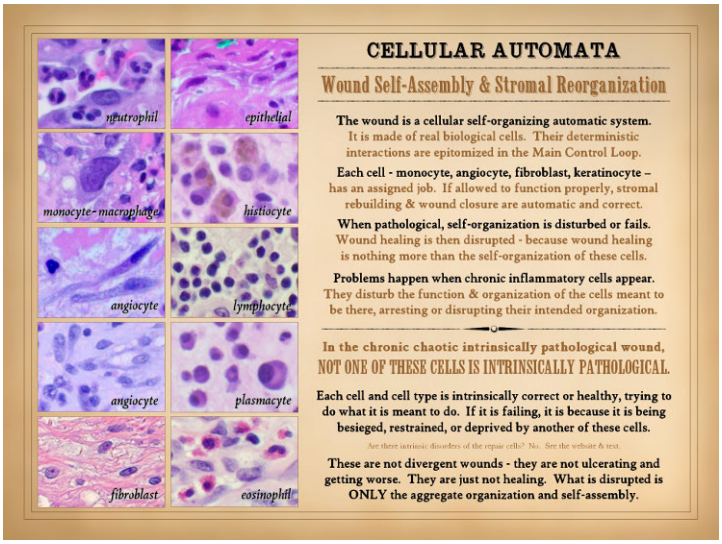
This discussion is front-and-center when understanding non-healing chronic-and-pathological CAP wounds. That subject is allied with the concepts of when not to operate, but they maintain some separate identity. Their conjunction is this. When wounds are operated on when they shouldn't be, when too much is done too soon and too often, these indiscretions might be on simpler more acute 2-population wounds, or else on more complex chronic 3-population wounds. Four scenarios are relevant:

1 - If operating improperly on healthier 2-population wounds (left pane), then inflammation and injury can ramp up, and the wound can fail to heal. However, back off, let the wound settle and recover, and things can heal. Wound healing remains inherently healthy, so eliminating the repetitive injury from surgical indiscretions allows the system to settle to its normal state of convergence.

2 - When operating improperly on CAP wounds (right pane), it is putting more fuel on the fire of an intrinsically non-healing system. Eliminating unnecessary or misguided additional trauma helps, but does not solve the entire problem nor ensure that things will then heal.

3 - The third aspect of this is that when repetitive injury continues to disrupt the wound, or sustain acute inflammation, thrombosis, and more injury, those are the circumstances which breed the third population and a non-healing CAP wound. Then, even after extrinsic injury ceases, the wound cannot heal. Thus, indiscretions of surgery, too much too soon too often, can do more than just delay healing and a good result. It can transform the wound such that it cannot heal even after injury is gone.

4 - For any wound, either 2- or 3-population, that is elevated into a dysdynamic attractor of repetitive injury, inflammation, thrombosis, and sustentation of altered dynamics, these are situations where very little additional provocation can have strong detrimental effects. Any added extrinsic injury, any errant or unindicated operation, new trauma applied too soon, failure to treat underlying disease or control wound inflammation and edema, these can be the proverbial "straw that breaks the camel's back", disrupting wound healing into the complications and failed results that are the focus of this presentation.



10

The biology of injury, inflammation, wound healing

Self-organization, dysdynamia, and the intrinsic health of the unhealthy wound.

This presentation about wound pathergy and clinical complications is focused on clinical care, not basic science. However, the science behind it all is crucial to understand why biological systems fail leading to wound pathergy, necrosis, ulceration, and related undesirable clinical events. This last slide in this short overview of wound science and wound pathology is meant to leave you with an important concept – that even when things seem to be going horribly wrong for a wound or patient, there is often nothing intrinsically wrong with the patient or constituent physiological systems.

The wound, i.e. the reparative events that mend the injured tissues, is simply a matter of stroma reorganizing itself. It is a process of self-assembly by the few types of biological cells which constitute the system. The rules or interactions which govern the process are functions of the interactions between nearby cells. As such, the wound is a self-organizing automatic system – a cellular automaton ("cellular" here being an abstraction of individual reactive elements in a population, a term from non-linear dynamics) – made of real biological cells.

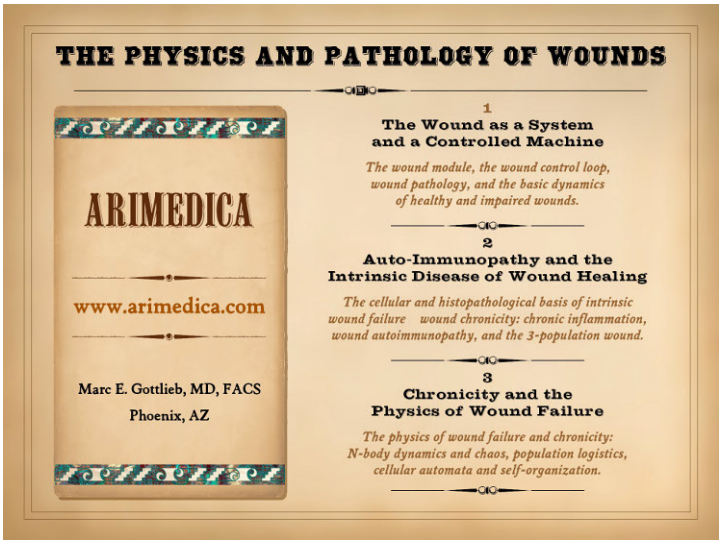
The photos are portraits of cells that participate in the healthy and the pathological wound. Each normal intrinsic cell - monocyte, angiocyte, fibroblast, keratinocyte - has an assigned job. If allowed to function properly, stromal rebuilding & wound closure are automatic and correct. When the wound or its cells are pathological, than self-organization is disturbed or fails, and wound healing is disrupted – because wound healing is nothing more than the self-organization of these cells. Problems happen when chronic inflammatory cells appear. They disturb the orderly function and organization of the other cells that are meant to be there, arresting or disrupting their intended organization.

The organization of the wound is an automatic event when all is healthy. When healthy and convergent, the wound dependably achieves an extremely stable final form from just a few basic rules or dynamics executed by a very small number of cell species. Once a wound is fully re-organized back to final scar-stroma-dermis-fascia, once it is fully converged, it is stable. Angiocytes and fibroblasts, vessels and connective fibers are then settled into their final positions and forms that will remain essentially unaltered for the remainder of the host's life. (Whatever remodeling subsequently takes place in the stroma is a long time-base or slow decay-rate event that is then part of normal basal biology, not part of the original automatic assembly of wound healing.)

When the wound is pathological and organization is disrupted, the system is still a group of cellular automata. The problem is that it cannot converge on the intended form. It remains in a loose state of quasi or unsettled organization, trying to organize but remaining mixed up, remaining glassy and amorphous rather than crystalline, fluid or flowable rather than solid, plastic rather than elastic. As "iterations" or time continue, the structure can keep reorganizing and re-morphing, with cells and structures appearing, disappearing, flowing, shifting, reshuffling. It will never be fully settled until adverse stresses or repetitive injury are controlled and the system is allowed to converge. Those stresses, the perpetuators of the wound, are extrinsic (continued disease, injury, inflammation, and thrombosis) or intrinsic (the dysdynamia that develops due to abnormal cell populations and population dependencies).

The "dysdynamia" we are talking about should be distinguished from conventional disease. From the clinical perspective, the non-healing wound is a "disease", a morbid state that interferes with health or function. However, the intrinsically pathological wound is not a divergent wound, not actively ulcerating and getting worse. It just is not healing. In the chaotic CAP wound, what is sick is just the collective interactions of otherwise healthy cells doing as they are programmed in response to extrinsic stimuli. What is disrupted is ONLY the aggregate organization and self-assembly. In the chronic chaotic wound, not one of the cells shown is intrinsically pathological. Each cell and cell type is intrinsically correct or healthy, trying to do what it is meant to do. If it is failing, it is because it is being besieged, restrained, or deprived by another of these cells. If it is abnormally overactive and thereby disrupting things, it is because something else is stimulating, up-regulating, or otherwise turning it on. None of these cells is sick. Each is acting correctly in response to altered inputs. Only their collective interactions are altered. From a clinical point of view, the system as a whole is sick. From a physics point of view, this is just the expected dynamically and thermodynamically mandated behavior of complex multi-control systems.

Dysdynamia of the system is the intrinsic disease of wound healing. Would it not be correct though to say that genetic or metabolic diseases of angiocytes or fibroblasts are themselves intrinsic diseases of this system? Yes, in principle. In actuality though, there are few if any such biological diseases. That may sound strange, given the spectrum and nature of other diseases that afflict the human condition. Nonetheless, there are few intrinsic genetic or cellular disorders of the stroma and wound repair cells. For an explanation, see slide #26 from Part 3 of the series referenced on Slide 11.



11
Further information

The preceding two slides are a short glimpse into a large subject about the physiology and pathology of wounds at a system level, specifically about how wounds fail to heal. From a system's point of view, the conventional biological details, rooted in biochemistry and cell biology are important, but not central. What is ultimately important is how the many individual cells and chemicals inter-operate with each other, and how they can become unbalanced to the point that the normal and nominal goals of the system, to get the wound healed, are subverted. The relevant science is non-linear dynamics, and this is the domain where physics and pathology intersect. Repetitive injury, thrombosis, inflammation, necrosis, and ulceration are at the core of wound failure and impaired wound healing. It is thus no coincidence that they are central to this discussion about wound failure and surgery complications.

For anyone interested in this, the whole subject is presented in detail in a set of studies and papers first presented in 2009 and 2010. These papers and supplementary materials are all available at **www.arimedica.com** . The main paper is a three part presentation that looks at wound pathology from the point of view of its applicable physics, elucidating the intrinsic dysfunctions of the wound as a result of dysdynamia, especially when stromal auto-immunization has occurred due to prolonged population admixture in a repetitively injured wound:

Part 1 – The Wound as a System and a Controlled Machine
The wound module, the wound control loop, wound pathology, and the basic dynamics of healthy and impaired wounds.

Part 2 – Auto-Immunopathy and the Intrinsic Disease of Wound Healing
The cellular & histopathological basis of intrinsic wound failure & wound chronicity: chronic inflammation, wound autoimmunopathy, & the 3-population wound.

Part 3 – Chronicity and the Physics of Wound Failure
The physics of wound failure and chronicity: N-body dynamics and chaos, population logistics, cellular automata and self-organization.

An earlier abridged version is also available:
(Not) Atypical Wounds
Autoimmunopathy and Connective Tissue Disorders: The True Intrinsic Diseases of Wound Healing

Current links to these and related materials are at:
http://www.arimedica.com/presentations.htm
http://www.arimedica.com/content/arimedica_wpp-1_wound%20control_gottlieb-me_maui-2010-0222_annotated.pdf
http://www.arimedica.com/content/arimedica_wpp-2_autoimmune%20&%20intrinsic_gottlieb-me_maui-2010-0222_annotated.pdf
http://www.arimedica.com/content/arimedica_wpp-3_chronicity%20&%20failure_gottlieb-me_maui-2010-0222_annotated.pdf
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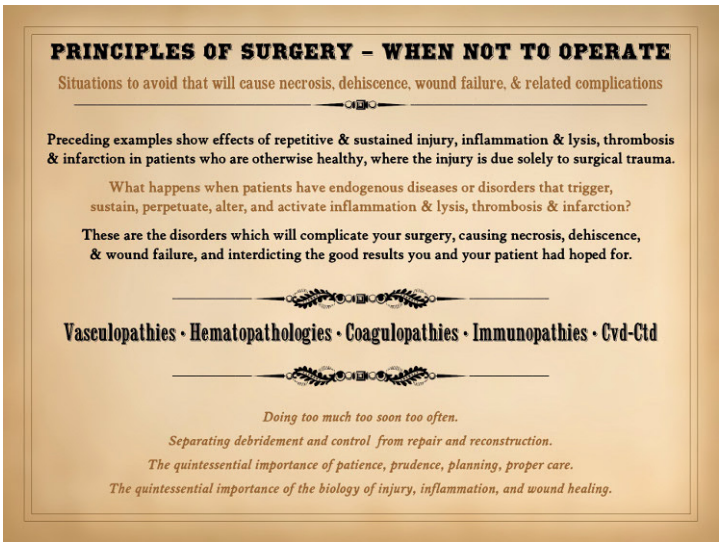


12
Wound dysdynamia and failure – the predisposing disorders

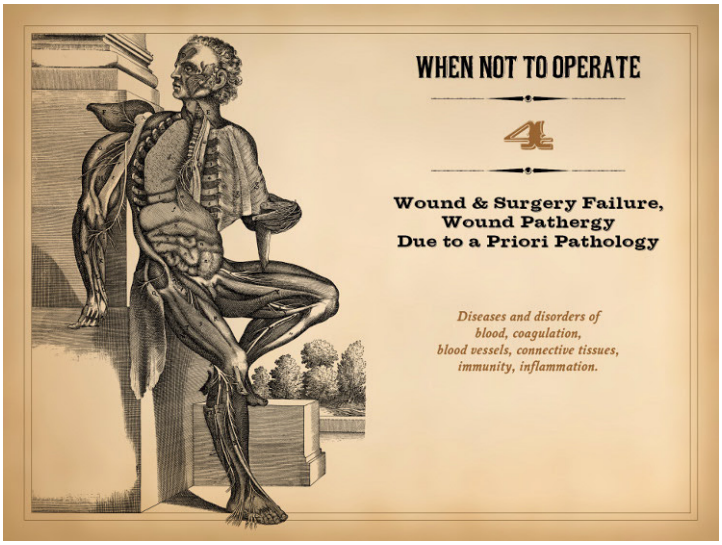
The preceding case studies demonstrated what happens when a surgeon does too much too soon too often, when surgical trauma is the sole instigator of injury, in patients who were otherwise healthy and free of wound healing disorders or ulcerogenic diseases. Repetitive injury stirs up a "hornet's nest" of injury, inflammation, and thrombosis, along with edema, indiscriminate fibrosis, and similar factors which amplify each other and ensure that the wound fails. Acute inflammation is destructive of tissues and inhibitory to wound healing. Thrombosis is infarctive and stirs up more inflammation. Et cetera. If a problem cannot be resolved within 2 or 3 short-interval procedures, then the surgeon must take a vacation from procedures and institute good basic wound and tissue care in order to get things back under control before more surgery can be attempted.

One can appreciate here the dichotomy of thrombosis and inflammation. They are a vital part of healthy biology, there to defend the host in conditions of assault and injury. Yet, it is their inherent nature to be damaging or destructive. Their effects are a matter of degree. Appropriate responses to "understood" stimuli protect the host, but overstimulation or amplification, or indiscriminant activity, or discordant timing, and the host is damaged. The problem gets worse

when the host systems are unbalanced or triggered by true pathologies, such as vascular or coagulopathic or immune disorders. That is the purpose of this overview, to explore their effects and understand how to accommodate them so that wounds and surgery are not harmed.

If wound dysdynamia and disruption is a problem for normal healthy people under errant circumstances, then what happens to patients who have pre-existing disorders that predispose to injury, thrombosis, and inflammation? What happens when a patient has an endogenous disease that can trigger, sustain, perpetuate, alter, and activate inflammation and lysis, thrombosis and infarction, without appropriate provocation and independent of physiological triggers? What happens when a patient has pathological wound healing, or an underlying ulcerogenic disorder (thrombo-infarctive type, inflammatory-lytic type, or both), or any other pre-existing or pathological condition of heightened inflammation, thrombosis, or necrosis? The problem for these patients is that these risks and their sequelae become evident not after 15 operations, not after 4 or 5 operations, not even after 2 or 3 operations. Their risks are a real and present danger with the first operation – indeed, even before the first operation, problems which may in fact be responsible for the situation that now requires surgery.

It is the ulcerogenic disorders and the diseases of wound healing which will complicate surgery, causing necrosis, dehiscence, and wound failure, subverting the good results hoped for by patient and surgeon alike. It is these disorders which require patience, prudence, planning, and proper care even before the first operation is done. Surgery is not disallowed, and when surgery must be done, it can be done safely with proper preparation and precautions. However, it can never be done naively, indiscriminately, and without preparation without risking necrosis, dehiscence, wound failure, & related complications. Which diseases are these? They are the diseases which cause vascular occlusion and thrombo-infarction, and those which cause inflammation, auto-immunity, and lytic ulceration. They are anything which can perpetuate the inter-dependent triad of injury, thrombosis, and inflammation. **They are predominantly the vasculopathies, hematopathologies, coagulopathies, immunopathies, and collagen-vascular connective tissue diseases.** This now brings us to the main subject of this presentation, when not to operate. When? In the face of these underlying diseases and disorders.

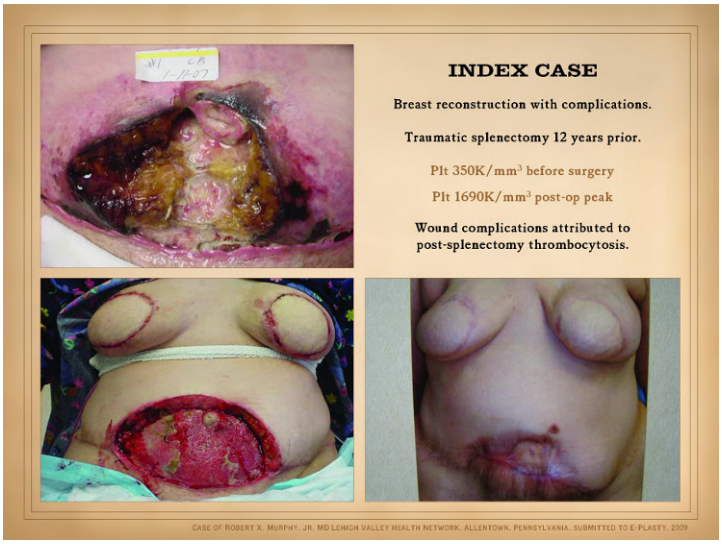


13
When not to operate – 4
Wound & surgery failure – wound pathergy – due to a priori pathology

The fourth reason not to do surgery is the issue of wound failure and wound surgery, i.e. wound pathergy, due to a priori pathologies. We have seen how repetitive rapid sequence trauma and surgery can stir up inflammation and thrombosis, so much that ulceration is promoted, wound healing is suppressed, and further surgery is guaranteed to fail. The only resurrection for the program of care and health of the patient is to back off of surgery and focus on the essential modalities of wound hygiene and control of edema and inflammation. This is true in patients who are otherwise the "picture of perfect health".

These same issues of wound failure and wound morbidity, with risks of surgery complications and sequelae are heightened in patients who have diseases that, independently and without proper provocation, ignite and stoke the flames of thrombosis and inflammation, causing infarction, lysis, progressive ulceration, and dehiscence and wound failure. The disorders that have these problematic effects are those of the blood, coagulation, blood vessels, connective tissues, immunity, and inflammation. This section will focus on the various diseases that carry these risks for wounds and surgery.

This is another illustration from Pietro da Cortona, Tabula VI, a view of the viscera in situ. Unlike the grimness and pathos of most of the figures in da Cortona's tabulae, this one has a certain sense of repose and contemplation, perhaps a hopeful indicator that with patience, prudence, and proper planning, that patients with these problematic disorders can nonetheless get safe and effective care.



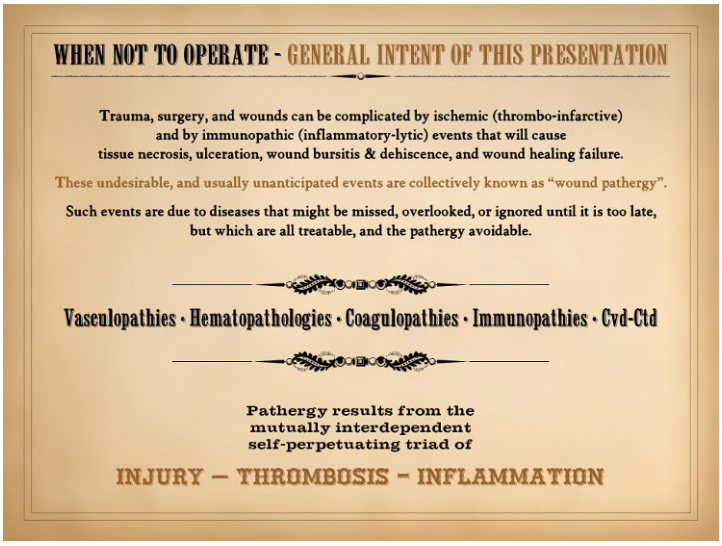
14
Index case – unanticipated wound necrosis

The problems and patients presented here the core of my own clinical practice – hence the wealth of case studies to draw upon. However, the impetus for this presentation on wound pathergy was a journal review. I was asked to review a paper submitted to the plastic surgery journal Eplasty, the case profiled here. It is a good example of the relevant scientific and clinical principles, and a convenient place to start this whole discussion.

The case is of a woman who had post-mastectomy bilateral breast reconstruction with TRAM flaps. As can be seen in the figures, the flaps were inherently healthy and the reconstruction is excellent. Had there been no wound and soft tissue complications, this is a result that any plastic surgeon would and should be proud of. The complications were obviously something unexpected, everyone caught unaware. They are also obviously not the mundane issue of simple flap ischemia and necrosis, which then implies that there must be some sort of hidden pathology. The patient had had a trauma splenectomy 12 years prior. During those 12 years she had no platelet problems, but after the necrosis started, it was observed that platelet counts rose from 350K/mm3 before surgery to a peak of 1690K/mm3 as the necrosis progressed. The infarcts were attributed to post-splenectomy thrombocytosis.

The issue we must address is that while the assessment of "post-splenectomy thrombocytosis" might have been correct, it was a diagnosis of assumption. It was not a properly analyzed and confirmed diagnosis, and it left unresolved a multitude of differential diagnoses that were more likely to be correct. Therein is the problem for the unwary surgeon, that if the spectrum of pathology for thrombo-infarctive and inflammatory-lytic events is not fully appreciated, then best care may not be instituted promptly and thoroughly, and the patient will get unnecessarily worse. The illustrations confirm that the patient eventually healed, but the report describes progressive problems after interim debridements and closure – she got worse before she got better (see slide #64). The problem of post-injury wound complications attributable to thrombosis, inflammation, etc. is referred to as "wound pathergy". That is the fourth reason not to operate and the central theme of this presentation.

Case of Robert X. Murphy, Jr, MD Lehigh Valley Health Network, Allentown, Pennsylvania, submitted to E-Plasty, 2009
Progressive Wound Necrosis Associated With Postoperative Thrombocytosis in Mastectomy and Immediate Breast Reconstruction Surgery: Report of a Case
Robert X. Murphy, Jr, MD, MS, FACS, Ginger A. Holko, RN, MBA, Afifi A. Khoury, MSN, CRNP, and Aaron D. Bleznak, MD, FACS
Journal ID: ePlasty Volume: 9. ISSN: 1937-5719 E-location ID: e34. Publisher: Open Science Company, LLC
http://www.eplasty.com/index.php?option=com_content&view=article&id=328&catid=170:volume-09-eplasty-2009&Itemid=69



15
Wound pathergy and its causes

The general intent of this presentation is to focus on wound pathergy and the underlying disorders that cause it, with the emphasis on (1) recognizing the spectrum of disease, (2) appreciating that they cause ischemic (thrombo-infarctive) and immunopathic (inflammatory-lytic) events that will cause tissue necrosis, ulceration, wound bursitis & dehiscence, (3) learning how they cause wound healing failure and create complications for wounds, trauma, and surgery, and (4) learning how to treat these problems, but especially how to anticipate and preempt them.

These undesirable, and all-too-often unanticipated events are collectively known as "wound pathergy". Such events are due to background diseases that are often missed, overlooked, or ignored until it is too late. However, they are all treatable. Pathergy and related complications are usually avoidable with patience, prudence, planning, and proper care, and post facto complications can likewise be stabilized quickly by the same treatments.

Pathergy results from the mutually interdependent self-perpetuating triad of injury – thrombosis – inflammation. As we have already seen, when these events become entangled, sustained, and self-perpetuating, then wound pathergy can complicate surgery in otherwise completely healthy patients. When patients have disorders which tend to indiscriminately cause thrombosis and inflammation, then the risks of wound pathergy and complications are substantially higher. What diseases cause these risks? The answer lies in a simple subsidiary question – what are the systems that normally control or affect thrombosis and inflammation? These are the vasculopathies, hematopathologies, coagulopathies, immunopathies, and collagen vascular diseases (connective tissue disorders – cvd-ctd). These disorders can spontaneously cause thrombosis and inflammation, infarction and ulceration - sometimes acutely and dramatically, sometimes chronically and insidiously. They can also have heightened

exaggerated reactions and risks when triggered by acute physiological stresses that normally elicit thrombosis and inflammation, such as infections, allergies, trauma, and surgery.

16
Set 1: ulcers due to thrombocytosis

Forthcoming are 30 case studies meant to illustrate the general categories of disease that cause wound pathergy and related problems. They are organized into several sets based on general concepts and categories of pathology.

Set 4 will focus on micro-occlusive and ulcerogenic complications of the hematopathologies (starting at slide 34). Ulcers and wound problems related to thrombocytosis are just a subset of those. A thrombocytosis case study was placed first, not because it represents a distinct category and not because it is the most common cause of pathergy (certainly not), but because it relates to the index case presented above. This is a good place to slide into a discussion of these disorders, especially because it affords a chance to study the clinical logic and analysis of evaluating such a case.

17
Platelets

In the index case presented, the history of splenectomy is a given, the reactive thrombocytosis is a given, and the wound infarcts are a given. Equating them together however was an assumption – possibly correct – but an assumption nonetheless. "Post-splenectomy thrombocytosis" was a logical starting place on the differential diagnosis, and this might even have ended up being a legitimate ***diagnosis of exclusion*** after other possibilities had been ruled out, but a blind ***diagnosis of assumption*** can rarely be justified. The key to understanding this case is to realize that the thrombocytosis could have been just a benign passive or reactive transient of no morbid significance, and the pathergy could have been due to any number of other factors – in fact statistics favor that the thrombocytosis was coincidental. In analyzing this specific case or any case of thrombocytosis related pathergy, it is worth knowing some of the basic statistics about thrombocytosis and risks:

Nominal thrombocytosis is defined by platelet counts over 400,000 or 600,000 or 1,000,000 (depending on type of problem, specific nomenclatures, author, and other circumstances). Thrombocytosis has two general categories, primary and secondary. Primary or "essential" thrombocytosis is one of the myeloproliferative disorders (the others being chronic myelogenous leukemia, polycythemia rubra vera, and myelofibrosis). Like other types of neoplasia, the primary type represents a pathological autonomy or deregulation of platelet production. Secondary thrombocytosis is an exaggerated reactive elevation of platelets, generally having some basis in normal regulatory physiology, due to some other primary pathology or stress, the common causes being trauma and surgery, infection and inflammatory states, and cancer and various other diseases.

What is the incidence of thrombocytosis and associated thrombotic or infarctive events? **(1)** Thrombocytosis after splenectomy is common, with an incidence of transient, persistent, or incidental thrombocytosis as high as 80%. **(2)** Thrombosis due to or associated with thrombocytosis is a well recognized phenomenon, but the incidence is low. **(3)** More specifically, the thrombotic and embolic complications of post-splenectomy thrombocytosis are only about 5%. **(4)** Even in myeloproliferative primary thrombocytosis, the disease is generally benign (with treatment), and the incidence of thrombosis or embolism is only about 10-15%. **(5)** Statistics of this sort attempt to correlate thrombosis rates with raw platelet counts, but remember that that is only part of the story. Platelet elevations can also imply a spectrum of possible intrinsic and extrinsic types of platelet dysfunction, and the incidence of associated thrombotic and also hemorrhagic complications vary with specific diagnoses.

Thus, while post-splenectomy thrombocytosis and thrombosis are basic textbook knowledge, the incidence of complications is low, and a problem as presented in this index case is unexpected. Given the low incidence statistics just mentioned, thrombocytosis may or may not have been the primary or only culprit that caused the necrosis. It is thus understandable that adverse risks and events might be underappreciated or unanticipated by a surgeon until it is "too late", after an event is initiated or minor damage progresses to major damage. That is especially true in this case, where pre-operative platelet counts were normal, and oncoming trouble was not foreseen. However, realize what it means to be a "diagnosis of assumption". The common causes of secondary reactive thrombocytosis are trauma and surgery, inflammation, etc. Under these circumstances, thrombocytosis is apt to occur or be exaggerated in a patient who has had a splenectomy. However, because thrombosis rates with thrombocytosis are low, all of the pathergy and necrosis could likely have been caused by some other overlooked disease. Simply put, post-splenectomy thrombocytosis under those conditions of stress was more likely to have been a consequence of the trouble, not the cause. If you

simply assume that the thrombocytosis is the cause of the necrosis, then you stop looking for the real demon, the occult underlying disorder.

The message is not to overlook the hidden disease. “Major damage” is avoidable – that is the goal of learning about all of this – and this is contingent on understanding the spectrum of pathology that can lead to wound pathergy. This case is a good one for understanding how to parse the pathophysiology of the events and make the correct diagnosis, a necessary prelude to proper treatment. In trying to decide if thrombocytosis versus something else was the culprit that caused the necrosis, there are a few concepts about platelet function worth remembering:

1 - Platelets are not just dust and debris, but rather active elements with complex functions programmed to respond to acute events. Not only do platelets adhere and aggregate, but they trigger plasma protein thrombosis, trigger inflammation, have various effects on vessels themselves, and even have an important role in initiating wound repair. Their function is highly connected to various proteins which likewise have multimodal roles, all leading to complex interactions with a broad spectrum of physiological effects. (Consider for example: (1) von Willebrand disease, in which hypocoagulable-hemorrhagic events are due to a factor deficiency which affects both platelets and clotting proteins; (2) heparin induced thrombocytopenia (HIT) in which severe thromboembolism is concurrent with low platelets; (3) myelofibrosis, in which low platelet counts can be accompanied by both hyper- and hypocoagulable states.) It is incorrect to think simplistically about thrombocytosis as a passive "log jam" of too many platelets and particulate sludge damming the small vessels, and that is why simple thrombocytosis without any triggers has a low incidence of thrombosis.

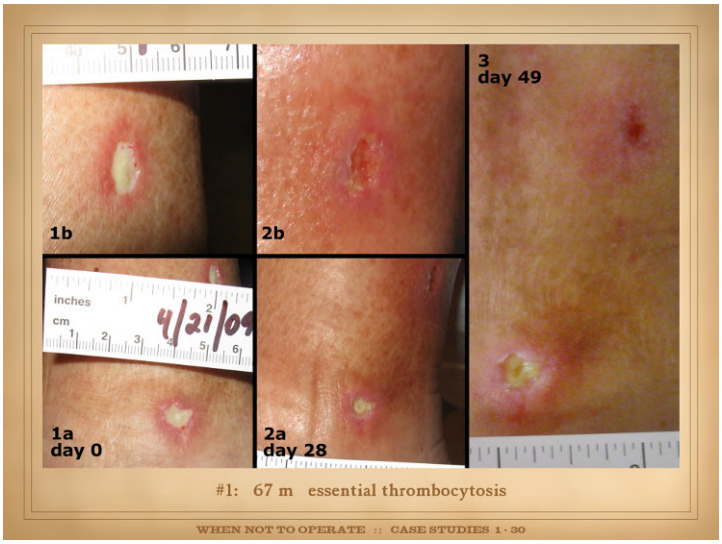
2 - Platelets are not always “on” and active. They exist as a reserve in “standby” mode, awaiting an undesirable event. Normal healthy platelets require a trigger to do their business. Even if platelet counts are high, random adhesion-aggregation-thrombosis is unlikely, explaining the low thrombosis statistics mentioned above. However, this is true only during baseline "healthy" status, absent potent triggers such as trauma or inflammation. Nominal thrombocytosis may seem completely benign during non-morbid periods, but once a trigger occurs, acute platelet events can be accelerated or amplified. Thus, abnormal high platelet counts become much more relevant during morbid states or when triggers occur (inflammation, trauma, surgery), even in patients who might have had benign thrombocytosis without incident for a long time.

3 - Thrombosis is not linearly related to platelet count, and risks and responses are not predictable by raw counts. Thrombotic risk obviously has some general relationship with platelet load, but the physiology is so complex that a one-to-one graph of platelet counts versus secondary events cannot be made. Because platelets are not “on”, but on “standby”, face value numbers are irrelevant until a trigger occurs. Once a trigger does occur, acute platelet activation is a strongly non-linear self-amplifying process that rapidly begets more platelet thrombus and protein thrombus. (As those who have done any microvascular surgery can likely all attest, "white thrombus" due to abnormal platelet aggregation occurs unexpectedly, generally in patients with normal platelet counts, and once it starts, it is difficult to control.) An a priori high platelet count can unbalance this system in ways which increase sensitivity or amplify, exaggerate, or accelerate the response once a trigger occurs. "Quorum sensing" may allow high platelet counts per se to lower their own threshold (increase sensitivity) to triggers that initiate their aggregation or to conditions of stasis and accumulation.

4 - Surgery and trauma are immediate and complex platelet triggers. Remember, surgery and trauma not only trigger platelet activity, they also upregulate platelet production and release from the bone marrow (in principle to balance or resupply the consumption of circulating platelets). This complex integrated system also releases leukocytes and other blood elements from marrow and reservoir areas, and it activates protein thrombosis (clotting). Thrombocytosis and thrombosis are not simply built into these events, they are the primary intent of these events, as long as they stay within quantitative bounds and confined to the area of injury. But this is a complex non-linear multi-control self-amplifying process which can leach into the general circulation and trigger thrombosis in remote areas. Healthy patients with “healthy protoplasm” keep it all in proper balance, but in extreme circumstances or in a priori unhealthy patients, keeping these events regulated and confined within physiological limits is less certain.

In summary, thrombocytosis per se can raise thrombotic or pathergy risks in principle, but the likelihood of morbidity and complications cannot be accurately anticipated on platelet counts alone, especially with platelet counts less than 1 million. Simple benign thrombocytosis has low risks. Risks increase during conditions of injury and stress which amplify or activate platelets. In wound pathergy such as the case presented, thrombocytosis is quite likely to have been a coincidence to or a consequence of the adverse events rather than the cause. However, even in someone who has had thrombocytosis without incident for a long time, a prior benign history is no guarantee of safety, and when the right trigger hits and the system cascades, the response can be dramatic. That is why a patient with thrombocytosis or the first signs of a related complication needs timely evaluation and treatment, to minimize subsequent damage.

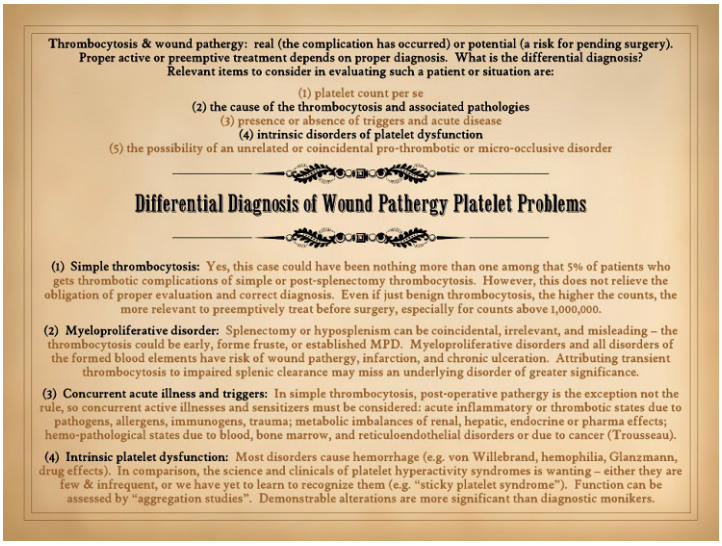
The following slide is the first in this series of 30 case studies of wound pathergy. It demonstrates the more common and mundane wound complications associated with thrombocytosis.



18
Case #01
(Set 1, ulcers due to thrombocytosis)
Illustrating the association of wound and soft tissue problems with thrombocytosis.

This 67 year old man had primary essential thrombocytosis. He was otherwise healthy, with a negative system review and risk profile for other thrombo-occlusive and ulcerogenic disorders. His platelet counts were maintained within normal ranges with hydroxyurea, but they would periodically rise and reach over 1 million, necessitating variable drug doses. Ulcers developed on the leg and ankle during an elevation of platelet counts above 800K. Basic topical wound care controlled gross inflammation and active ulceration, but a proliferative wound module failed to appear, even with platelet counts restored to normal, a failure attributed to the wound healing negative effect of hydroxyurea. Wound healing began after switching to anagrelide instead of hydroxyurea, and after starting wound stimulatory topical therapy with PDGF (platelet derived growth factor). This is the most common presentation of thrombocytosis associated chronic wounds, multifocal small ulcers on the distal leg, ankle, and foot. Surgery for those ulcers or other reasons around the ankle is at risk for dehiscence and ulceration, but that does not imply a categorical generic risk for surgery elsewhere.

Figure 1a (day 0) shows two ulcers on the left lateral leg; the inferior one is over the malleolus; the superior one is shown closeup in **figure 1b**. They are shown a month after the thrombocythemic episode that caused them, after a month of hygienic wound care and stabilization of platelet counts. Inflammation and active ulceration have been controlled, but the ulcers remain wound healing incompetent. **Figures 2a, b** (day 28) are the same views one month later after the switch to anagrelide and PDGF (the two views are shown at the same scales as their counterparts in figure 1). The malleolar ulcer has contracted, and the upper ulcer has developed a complete wound module including epithelial ingrowth. **Figure 3** (day 49) shows that three weeks later the upper ulcer is nearly healed. Because the lower ulcer perforates into the malleolar bursa, it cannot close any more without other intervention, but it has remained stable and symptom free, along with platelet counts stable around 200K.



19
Applied differential diagnosis

In the index case, thrombocytosis was real, but it was a mistake to blindly attribute it solely to the post-splenectomy status, and a mistake also to attribute the wound complications solely to the thrombocytosis. Consider next any situation of thrombocytosis and wound pathergy, either real complications already occurred or the anticipation of potential risks for pending surgery. Effective treatment, active or preemptive, depends on proper diagnosis. What then is the proper differential diagnosis for platelet associated wound pathergy?

"Proper differential diagnosis" begins by considering the spectrum of disease for the putative problem. A conceptual framework of physiological and pathological alterations must be organized, then that must be cross-correlated with diagnostic studies and known nosological and syndromic pathology. For the index case where platelets were implicated, the conceptual framework for analyzing platelet complications would be the following 5 general concerns and categories of pathology:

(1) Platelet count per se: As discussed, platelet counts are important, but counts per se are a low risk for thrombosis, and thrombotic risk cannot be directly correlated with raw platelet counts. However, remember the importance of the injury-thrombosis-inflammation triad. Surgery triggers these events, and the vascular stasis that occurs at the margins of a flap or incision can trigger these events. These factors could therefore themselves have caused the problems presented in the index case, and indeed, flap and wound complications happen now and then to seemingly normal people for no other apparent reason (or are they really normal? and will the real culprit reveal itself if you look for it?). In a patient with an otherwise benign thrombocytosis, there could certainly be an exaggerated response to these normal triggers. So yes, it is true, that this case could have been nothing more than one among that 5% of patients who gets thrombotic complications of simple or post-splenectomy thrombocytosis, occurring in response to an appropriate physiological trigger (injury) or to the conditions of low flow and stasis that are inherent to fresh flaps. However, this possibility does not relieve the obligation of proper evaluation and correct diagnosis. And even if it is just simple thrombocytosis, the higher the platelet count, the more relevant it is to preemptively treat before surgery, especially when counts exceed 1,000,000.

(2) Cause of the thrombocytosis and associated pathologies: Regardless of the platelet count per se, a correct diagnosis must be made as to the cause of the thrombocytosis. Secondary causes, passive, reactive, compensatory are those due to the trauma-surgery-injury, or due to the

post-splenectomy status, or due to an intercurrent illness such as cancer or chronic infection or allergic-immune state, etc. A splenectomy history is obvious, but the whole point of this discussion is that one cannot blithely assume that "the obvious is the culprit", especially when "the obvious" has low risks for complications. Other or occult causes of secondary thrombocytosis must be considered, keeping in mind that "secondary thrombocytosis" might be a positive diagnosis if a causative gremlin is found, else a diagnosis of exclusion if no culprit is uncovered. If the thrombocytosis is not a secondary reactive or compensatory state, then primary thrombocytosis must be considered, the autonomous or neoplastic or proliferative type, the myeloproliferative disorders. Making the correct diagnosis may not be so clear. For starters, the myeloproliferative disorders like many diseases have a gradient of severity and risks. If platelet counts hover at the low end around 600,000, then a diagnosis of chronic essential thrombocytosis can be marginally certain. Also, a myeloproliferative disorder can occur in a patient who coincidentally has had a splenectomy or hyposplenism, and MPD should be considered especially if the thrombocytosis is high, persistent, or of late onset after the splenectomy. In less severe forms, where platelets and megakaryocytes remain responsive to normal controls, then normal triggers for reactive thrombocytosis, e.g. surgery, can have an exaggerated response. Whatever the ultimate conclusion is about the cause of thrombocytosis, it bears on your assessment of infarcts and pathergy. Myeloproliferative disorders and all disorders of the formed blood elements have risk of wound pathergy, infarction, and chronic ulceration (sickle cell ulcers are a paradigm that most physicians are probably aware of). Simple hyposplenism has much less of those risks, and thus, in a case of actual pathergy, attributing thrombocytosis solely to impaired splenic clearance may miss an underlying disorder of greater significance.

(3) Concurrent acute illness and triggers: To reiterate, surgery and flow stasis initiate injury-thrombosis-inflammation, and preexisting thrombocytosis could augment this in principle. Nonetheless, in patients with simple thrombocytosis, post-operative wound pathergy is the exception rather than the rule, so concurrent active illnesses and sensitizers must be considered. This includes: any acute inflammatory or thrombotic state due to pathogens, allergens and immunogens, or trauma; metabolic imbalances due to renal, hepatic, and endocrine disorders, or due to drug effects; hemo-pathological states due to blood, bone marrow, and reticuloendothelial disorders or due to cancer. It is worth mentioning Trousseau's syndrome, thrombotic events associated with cancer, usually colon, pancreas, lung, and other visceral carcinomas. This tends to occur in late invasive or metastatic disease, often when the tumor itself is still occult or subclinical (it does not apply to the index case presented, breast stage IIa). The classic syndrome describes venous thrombosis and macro-arterial events, but skin infarcts, chronic ulcers, wound pathergy, and thrombotic complications of surgery are very real issues in this syndrome, and recent onset leg ulcers or skin pathergy and necrosis after minor trauma can be the presenting symptom of late stage cancers.

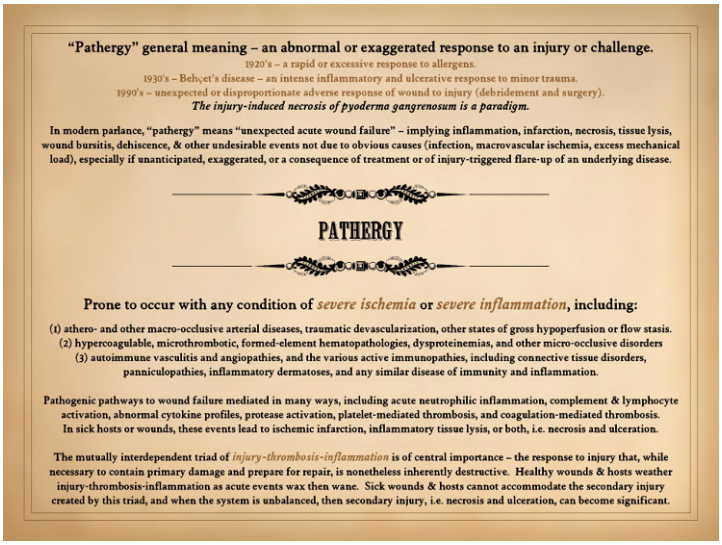
(4) Intrinsic platelet dysfunction: As we have discussed, high counts of otherwise normal platelets might or might not by themselves carry thrombotic risk. What happens though when the platelets are not normal – altered, pathological, dysfunctional? Intrinsic dysfunction of platelets occurs commonly enough, but the majority of disorders and syndromes that are commonly appreciated are those that result in hemorrhage (e.g., von Willebrand, hemophilia, Glanzmann, adverse or therapeutic drug effects). Analysis of a situation is muddied further because many nominally thrombopenic-hypoactive-hemorrhagic platelet disorders also have some thrombotic risk. However, in comparison to the hypoactivity-hemorrhagic problems, the basic science and clinical knowledge of platelet hyperactivity syndromes is wanting. Either such diseases are few and infrequent, or we have yet to learn to recognize most of them. One oft-mentioned condition is the "sticky platelet syndrome", but this is debated as to whether it is a distinct genomic or metabolic entity, versus a dynamical expression of weak platelet alterations coupled to acute triggers. Fortunately, even in the absence of robust knowledge or a strict nomenclature, platelet functions and over-activity can be assessed in the laboratory. "Aggregation studies" depend on triggering platelet activation with chemical triggers such as epinephrine, ADP, or collagen, thereby mimicking normal in vivo events (platelet aggregometry is used most commonly to monitor therapy with platelet inhibitory drugs such as aspirin or clopidogrel). Obviously, demonstrable alterations of function are more significant than any simple diagnostic moniker.

(5) Concurrent hypercoagulable, pro-thrombotic, or micro-occlusive disorder: Just because platelet counts are high, and even if there is some degree of platelet dysfunction or intercurrent trigger illness, it is a mistake to overlook the possibility that infarcts and complications were actually due to some other disorder. As discussed beginning on slide 28, these other disorders are generally those of immunity and inflammation, vascular disease, and hematopathologies. These chronic or occult illnesses all trigger the injury-thrombosis-inflammation triad unexpectedly or to excess, leading to tissue infarction (the vascular and micro-occlusive components) or tissue lysis and ulceration (the immune and inflammatory components). They are the hidden bogeymen of wound pathergy, lying in wait for unsuspecting trauma, surgery, and surgeons to unmask their nefarious effects. Among the thrombo-occlusive infarcts of hematological origin, there are those due to platelets, those due to the cells and other formed elements of the blood, and those due to the plasma protein coagulation system. Platelet adhesion and aggregation have received much attention in recent years due to their adverse effects on angioplasties, micro-vascular anastomoses, and stents and other vascular endo-prostheses. However, "in the wild", plasma based hypercoagulopathies are of much greater incidence as occult causes of chronic ulceration and wound pathergy. Because of the complex interactions between platelets, plasma, injury, and inflammation, alterations of one can affect alterations of another, lowering trigger thresholds, or amplifying reactions. When presented with a case of clinical wound pathergy, workup and diagnosis of the situation are not complete until you have a positive diagnosis, and that means ruling in or out each of these relevant risks and possible disorders.

For any situation of pathergy or any other strange and significant complication, this same type of reasoning should be applied to whatever might be the suspected primary pathology or underlying disorder. If a polycythemia was present, then one would have to analyze the differential diagnosis of erythrocytosis or leukocytosis. If a hypercoagulable state was present, one would have to run the full spectrum of possibilities to find the specific culprit (e.g. intrinsic prethrombotic proteinopathies versus immune procoagulants versus toxic-metabolic effects). If some sort of dysproteinemia was present in serum or plasma, then the differential diagnosis for that situation would have to be parsed (e.g. cryo-proteinopathies versus gammopathies, etc.). Blind assumptions of association, such as "post-splenectomy thrombocytosis" can be overly convenient, leading you to ignore the diagnostic and intellectual rigor required to correctly identify and confirm the true problem.

20
Set 2: Pathergy and pathological wound complications

Now that we have seen an example of wound pathergy related to the lead-in case, it is time to take a more rigorous nomenclature or nosology oriented view of the subject of wound pathergy. This begins with a general discussion of what pathergy is, and what is implied in the concept of "pathological wound complications".



21
Pathergy – a concept

"Pathergy" has the general meaning of an abnormal or exaggerated response to an injury or challenge. The term appeared in the early 20th century to describe rapid or excessive responses to allergens. In describing his eponymic syndrome, circa 1920-30, Hulusi Behçet, a Turkish dermatologist, extended the concept to include an intense inflammatory and ulcerative response to minor skin trauma. It has since accrued a broader meaning, signifying any unexpected or disproportionate adverse response of wound or periwound to accident, disease, or deliberate injury (debridement and surgery). The injury-induced necrosis of pyoderma gangrenosum is a paradigm.

In modern parlance, "pathergy" is synonymous with "unexpected acute wound failure". It is a tokenized way to describe progressive inflammation, infarction, necrosis, tissue lysis, wound bursitis, dehiscence, and other undesirable wound complications that are not due to obvious mundane causes such as infection, macrovascular ischemia, or excess mechanical load, especially if the problems are unanticipated, exaggerated, or a consequence of treatment or of injury-triggered flare-up of an underlying disease.

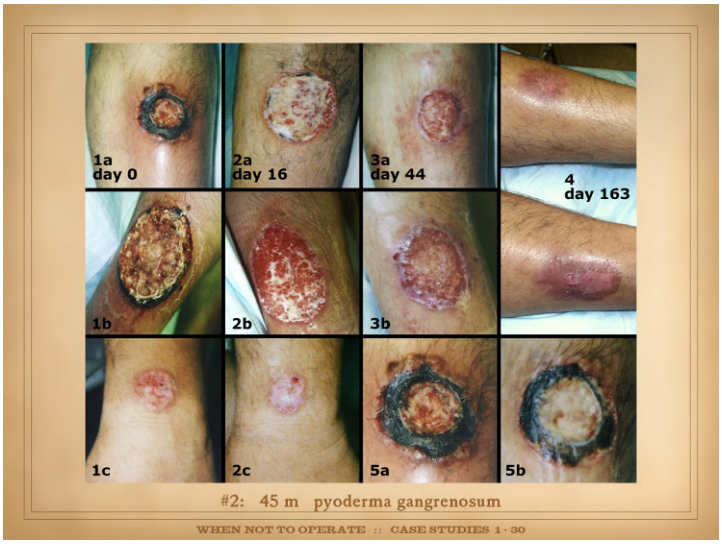
Wound pathergy is most prone to occur with any condition of severe ischemia or severe inflammation. These include:

(1) Athero- and other macro-occlusive arterial diseases, traumatic devascularization, and other states of gross hypoperfusion or flow stasis (including "bad flaps").

(2) Hypercoagulable, microthrombotic, formed-element hematopathologies, dysproteinemias, metabolic and degenerative micro-angiopathies, and other micro-occlusive disorders.

(3) Autoimmune vasculitis and angiopathies, and the various active immunopathies, including connective tissue disorders, panniculopathies, inflammatory dermatoses, and any similar disease of immunity and inflammation.

In these disorders, the pathogenetic pathways to wound failure are mediated in many ways, including acute neutrophilic inflammation, complement and lymphocyte activation, abnormal cytokine profiles, protease activation, platelet-mediated thrombosis, and coagulation-mediated thrombosis, to name a few of these pathologies that are best understood. In sick hosts or wounds, these events lead to ischemic infarction, inflammatory tissue lysis, or both, i.e. necrosis and ulceration. It is crucial to understand and reiterate the central significance of the injury-thrombosis-inflammation triad. This response to tissue injury is necessary to contain damage, protect the host, and prepare for repair, but it is nonetheless inherently destructive. Robustly healthy wounds and hosts weather injury-thrombosis-inflammation as the acute events wax then wane. Sick wounds and hosts do not have sufficient physiological degrees of freedom to accommodate, filter, or mitigate the secondary injury created by this triad, and when the system is unbalanced, then secondary injury, i.e. necrosis and ulceration, can become quite significant. ***In these disorders, every injury or surgical procedure, from simple debridements and biopsies, even just needle sticks (Behçet's "pathergy test"), through any major trauma, incision, flap, and wound closure, is at risk for necrosis, lysis, dehiscence, and ulceration.***



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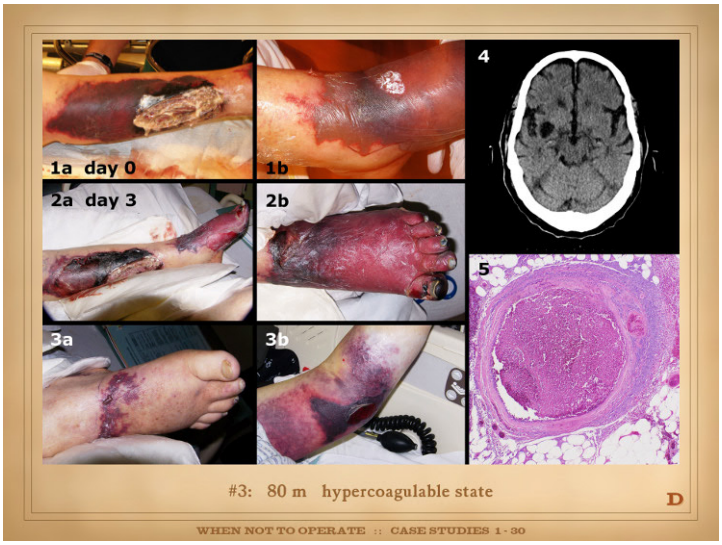
Case #02
(Set 2, pathergy & pathological wound complications)
Illustrating the basic concept of wound pathergy.

This is a 45 year old man with recurrent and persistent multifocal ulcerations of leg, trunk, and upper extremity. The lesions have the typical stigmata of pyoderma gangrenosum, especially the involvement of skin per se, sparing the subcutaneous panniculus. Biopsy was also consistent, showing an intense neutrophilic infiltration. Acute disease was resolved with intralesional and oral steroids. The disease remained under control as the patient was transitioned off of steroids and onto sulfasalazine, and the wounds began normal proliferation. He was healed and stable 4 months after the start of proper treatment. The aforementioned biopsy was taken before consultation, "bare" without the protection of steroids, and the effects are seen in the photo as a ring of black eschar surrounding the initial debridement – paradigm wound pathergy (and a prototypical feature of pyoderma gangrenosum).

Figures 1a, b, c (day 0) show lesions of left leg, right leg, and wrist at the time of consultation. Note the cutaneous eschar but preservation of viable adipose. **Figures 2a, b, c** (day 16) show the same lesions after initiating treatment. Disease has not progressed, eschar is now gone, and a wound module has appeared. **Figures 3a, b** (day 44) show the same leg lesions after several weeks. Wound healing, both contraction and epithelialization are active, and pathological changes are absent. **Figure 4** (day 163) shows the legs fully healed and maturing. In **figure 5a**, a close up of the original left leg lesion (day 0), note the edema and erythema around the wound, and the progressive necrosis at the superior margin. In **figure 5b** at 9 days, there is eschar from prior infarction, but edema and active necrosis are subsided after starting treatment. The ring of old eschar is the progressive infarction that occurred when the smaller original lesion was excised or biopsied.



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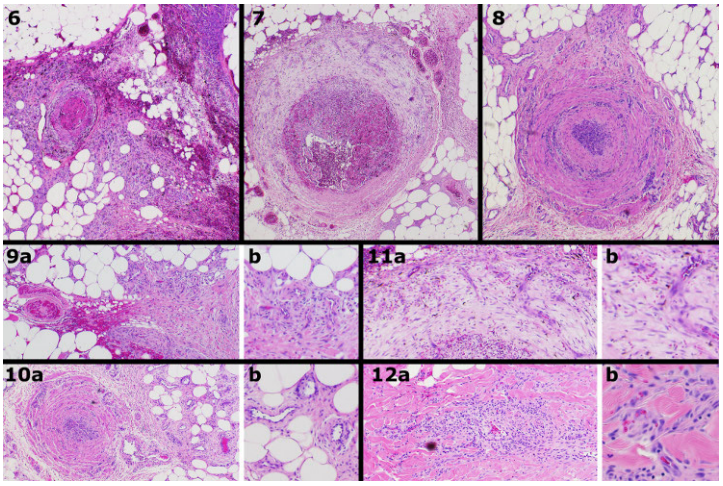
Case #03
(Set 2, pathergy & pathological wound complications)
Illustrating the risk and severity of wound pathergy.

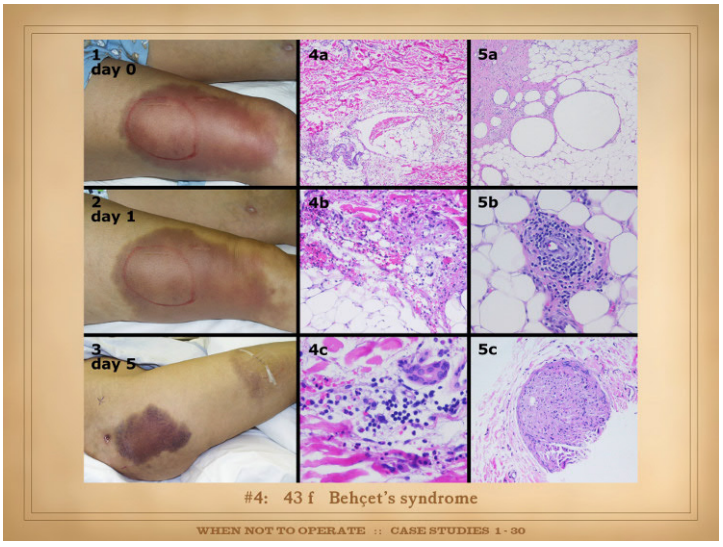
This 80 year old man had recurrent skin infarcts for 5 years. These events, often accompanied by confusion and mental status changes, were usually heralded by an inflammatory or traumatic event, such as urinary infection, viral upper respiratory illness, and bruises or cuts. He had been treated with warfarin, with difficulty regulating the dosage. The terminal event, which followed a period of warfarin instability, began with the onset of mental status changes and new skin infarcts on the legs and feet, both more severe than usual. Large and central vessels were patent (including cerebral and coronary vessels). Head CT scan showed chronic cerebral atrophy with signs of prior vascular events. Acute oliguria and rise in creatinine also occurred, without overt cause. One of the leg lesions was excised for histology, promptly triggering extensive new periwound stasis and infarction. The histology confirmed acute and chronic thrombosis. Further workup revealed deficiencies of proteins C & S and antithrombin-3, with alterations of other thrombosis-related proteins. Total and gamma proteins were low, but with high kappa and lambda light chains (the patient died before these results were available, thus urinary Bence-Jones proteins were not measured). The patient was started on heparin anticoagulation, and in spite of using a closely monitored and regulated protocol, he died from an event of acute back pain, hypotension, and anemia, presumed to be retroperitoneal hemorrhage. This case illustrates the complexity and multi-factorial risks of pathergy prone diagnoses: an a priori pre-thrombotic hypercoagulable state; thrombo-infarctive events associated with warfarin variations; known pathergy from trauma and inflammation; possible myeloma or light chain disease. This case also demonstrates that when the coagulation system and its many intricate physiological interconnects fall into a pathological attractor (i.e. become severely unbalanced), then hyper- and hypo-coagulable events can occur concurrently (see case #6).

Figure 1a (day 0), the medial left leg shows the excision site of an initial smaller lesion. That excision triggered progressive infarcts with complete necrosis at the margins (the dark black areas), and a wider zone of vascular stasis (blistered areas) which might recover with treatment. Underlying muscles and neuromuscular function were normal. **Figure 1b** shows the ankle and dorsal foot with similar changes, mostly ischemic blisters. **Figures 2a, b** show the same lesions 3 days later, after therapy with anticoagulants, steroids, rheological agents, and hyperbaric oxygen. The leg lesion and toes have progressed to complete necrosis, but the foot is largely viable, anticipating a transmetatarsal amputation (but the patient died shortly after these images). **Figures 3a, b**, the right foot and left medial elbow show similar lesions with mixed patterns of progressive damage or recovery. **Figure 4** shows a defect in the basal ganglia, a consequence of prior vascular infarction. Compare these images to the complications of common atherosclerosis, carotid and ilio-femoral disease, in which total leg gangrene and hemispheric strokes are expected, i.e. events in larger vessels. In the coagulopathic disorders, dramatic acute events can also happen, but the problems tend to be smaller and multifocal, more insidious and chronic, damage often being prolonged and cumulative. **Figure 5**, from the excised specimen seen in

figure 1a, shows acute thrombosis in a large subdermal vessel, including necrosis of the vessel itself. Histology revealed other features of this disease as seen in the addendum images below. They emphasize that insidious risks are the norm for many micro-occlusive disorders, a consequence of chronic recurrent subtle overlooked events. In cases of microthrombosis, wound pathergy, and other peculiar surgical complications, histologic examination of affected tissues often reveals the complexity of the problem, avoiding oversimplified nominal diagnoses such as "post-splenectomy thrombocytosis". These and the other micrographs shown throughout this review are meant to emphasize that ***unanticipated surgical complications and pathological wound events are due to demonstrable anatomical disease***. A surgeon ignores these diseases at the patient's peril.



Addendum images: These additional histology pictures (also from the original excised leg specimen) show additional findings beyond just the thrombosis and necrosis seen in figure 5. Figure 6 shows acute thrombosis and vascular stasis, with hemorrhage and necrosis in the adjacent tissues. What is peculiar is the degree of cellularity and hypertrophy in the surrounding septae of the hypodermis. As seen in the further pictures, this is angioid and fibrous stroma, not inflammation. (In thrombo-occlusive infarcts, inflammatory cells cannot be transported into the zone of injury thus acute inflammation is not seen.) **Figure 7** shows a large vessel in which chronic thrombosis and reorganization are accompanied by acute thrombosis in smaller surrounding vessels. Note the peculiar thickening and delamination of what should be the muscularis, and also the hypertrophy and fibrosis of surrounding septae. Figure 8 is another large vessel having a dense infiltration of angioid cells within concentric layers of thrombosis and reorganization. Note too the high density of small vessels within the thickened stroma around the large vessel. **Figures 9, 10, 11, 12** are all have a wide (**a**) and a closeup (**b**) view to show what the cells look like, mainly to emphasize that there are no inflammatory cells. Instead, the cells are all regenerative mesenchyme or matured stroma. **Figure 9** shows acute thrombosis and necrosis in a smaller vessel. In adjacent areas of septal hyperplasia there is solid angioid tissue with a high density of organized capillaries, just as would be seen in normal proliferative wound healing (reparative or "granulation" tissue). **Figure 10** shows another large vessel with concentric layers of hyperplasia and organization. It is densely peppered with small new vessels, both within itself and outside in the surrounding hyperplastic septae. The hyperplastic areas are angioid and fibrous stroma without acute or chronic inflammatory cells. **Figure 11** is a closeup of the vessel in figure 7, showing diffusely migratory spindle shaped angiocytes in ground substance matrix, with dense reorganization into mature vascular conduits. This is normal reactive (wound healing type) angiogenesis being overdriven. **Figure 12** shows the papillary-reticular boundary in healthy dermis outside the infarct zone. The sub-papillary vessels are not normal, with (1) diffuse cellular hyperplasia consistent with unregulated angiogenic stimulation, and (2) normal cell morphology consistent with reorganizing vessels in any wound. What all of these images show, in addition to the obvious thrombosis and necrosis, is that there is chronic diffuse angioid and stromal hyperplasia. This is probably the result of chronic "wound healing" proliferative activity which was stimulated by angiogenic cytokines, which were released by platelets or inflammation, which were induced by chronic persistent microvascular thrombosis. It all implies that during the several years of overt skin infarcts that this patient had, that there was also a background of low level subclinical events and pathological activity.



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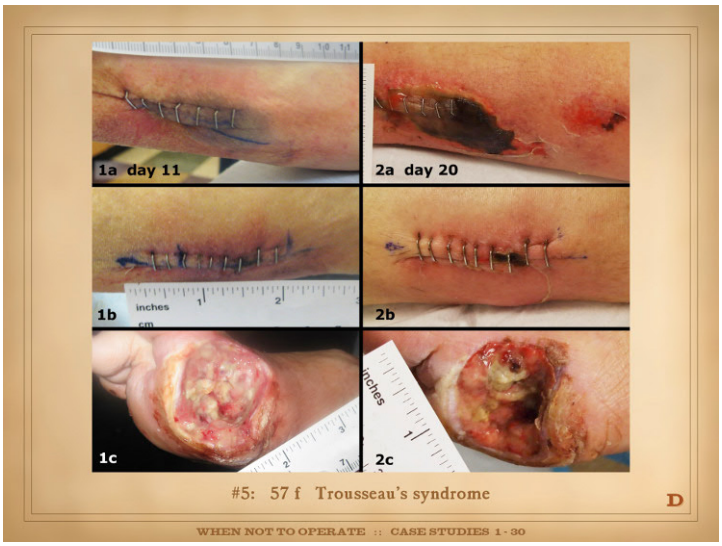
Case #04
(Set 2, pathergy & pathological wound complications)
Illustrating wound pathergy, Behçet's disease, and severe responses to even minor injury.

This case illustrates an even more unexpected and disproportionate tissue-destructive response to injury. This 43 year old woman was given a therapeutic injection near the hip (the drug was a common safe narcotic pain medicine). The injection site became ulcerated and widely bruised, with extensive fat necrosis deep to the skin. When seen in consultation, the diagnosis was made directly from a relevant history and physical. Of Lebanese origin, her intake inventory was positive for many signs and symptoms of an immunopathy, including oral and genital ulcers and ocular symptoms. This profile is not only pathognomonic of Behçet's syndrome, it is what defines the syndrome. Illustrated is the textbook Behçet's "pathergy test" in which the lateral thigh was given the most trivial of traumas, a single prick with an 18 gauge needle. At 12 hours after the needle, the surrounding skin appears widely bruised. The ability to do safe surgery without further pathergy depends on the use of corticosteroids. Under cover of intravenous methylprednisolone, oral prednisone, and intracutaneous triamcinolone, the patient had biopsy of the needlestick site and operative excision and repair of the hip wound. Histology confirmed that this was a complex inflammatory reaction, not just ecchymosis, with hemorrhage and mixed inflammation at the boundary between dermis and hypodermis. While there are some neutrophils, the reaction is predominantly mononuclear, with lymphocytes, plasma cells, and monocytes. Chronic peri-arteritis and unusual features such as membrano-cystic degeneration of the fat are not unique to Behçet's syndrome but nonetheless distinctive. With sustained anti-inflammatory therapies, all wounds healed without further complication.

Had the original injection site reaction on the buttock been recognized for what it is and treated accordingly, the rest of this story would not have happened.

Figure 1 (day 0) shows the results of Behçet's pathergy test 24 hours after a needlestick in the center of the marked circle. **Figure 2** (day 1) is another 24 hours later, after starting high dose steroids. The "ecchymosis" has not enlarged, and edema and scarlet erythema in the lesion have waned. Note the scar on the opposite knee, typical of many she had from prior lesions. In **figure 3** (day 5), the thigh lesion is already resorbing the acute changes, and the biopsy done 4 days earlier has had no complications. On the buttock is the ulcerated original injection site injury and surrounding reaction, and they are benign, uninflamed, and beginning to heal (this photo taken just prior to excision and closure of this wound). **Figure 4** shows the distinctive histologic features from the thigh 24 hours after the pathergy test needlestick: **(a)** mixed hemorrhage and inflammation at the dermal-hypodermal boundary, confirming that this is not simple ecchymosis, **(b)** a closer view showing plasma exudates and mixed cell infiltration, without suppuration or other generic acute inflammation spilling indiscriminately into the adjacent fascias, **(c)** a closer look at the cell mix, some neutrophils with many lymphocytes and monocytes. **Figure 5** shows distinctive histologic features in the original chronic hip ulcer: **(a)** membrano-cystic degeneration of the fat, seen with many immune panniculopathies, **(b)** chronic (non-neutrophilic) peri-arteritis, **(c)** chronic organization and fibrosis within a vessel, attesting to the thrombotic component of the pathology that caused the original ulceration.



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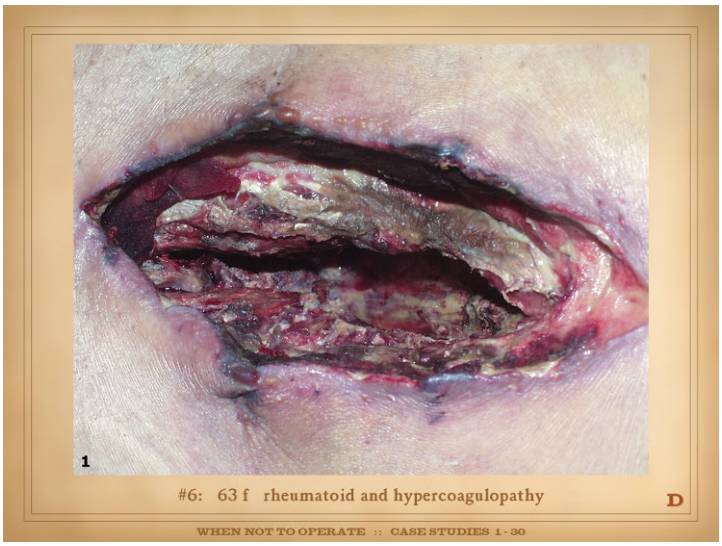
Case #05
(Set 2, pathergy & pathological wound complications)
Illustrating wound pathergy, occult disease, and Trousseau's syndrome.

This 57 year old woman had diabetes mellitus. She presented with typical mal perforans ulcers under the metatarsal heads in conjunction with significant peripheral neuropathy and ankle equinus due to achilles shortening. She had good pedal pulses and triphasic dopplers. She gave no history nor symptoms of gastro-intestinal disorder. Debridement and arthrectomy were done, accompanied by simple achilles lengthening through short incisions on the calf. Ten days after surgery, the otherwise uncomplicated leg incisions and periwound became cyanotic. This progressed to infarction of the surrounding skin. Laboratory evaluation for micro-thrombotic disorders was initiated, but it was never completed, because a few days later she had a rectal bleed. This was her presenting event for liver-metastatic colon carcinoma, and she died within 2 months.

Figure 1 shows the posteromedial aspects of the right **(1a)** and left **(1b)** legs 11 days after simple achilles tendonotomy. Although the incisions looked normal and healthy for the first week after surgery, and although no complications would be expected, especially in a patient with normal pulses, nonetheless both incisions show signs of ischemia and vascular stasis. The debrided MP joint **(1c)** still looks healthy. At 20 days, **figure 2**, the left calf incision has recovered **(2b)**, but on the right **(2a)**, there is progressive ischemia and infarction. Small infarcts have also appeared in the metatarsal wound **(2c)**. This is the style of pathergy that can afflict innocent incisions, typical of pyoderma, Behçet's, arteriopathies, various formed-element hematopathologies, and paraproteinemias, including cancer-related Trousseau's syndrome.

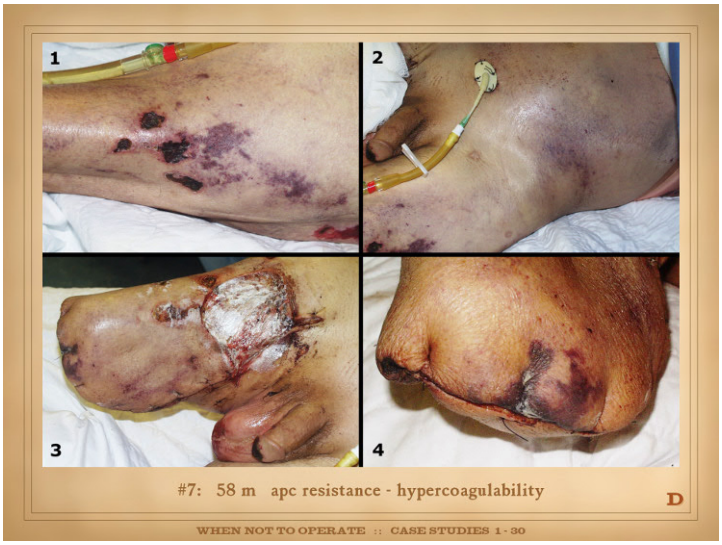


26
Case #06
(Set 2, pathergy & pathological wound complications)
Illustrating wound pathergy and serious patient risk.

This 63 year old woman had decompressive laminectomy of the lumbar spine for complications of active rheumatoid arthritis. Over the first few days after surgery, the incision and periwound became cyanotic, then necrotic. The photos demonstrate extensive necrosis of muscles and fascias as well as the skin. This is wound pathergy. For an elective incision on the trunk to behave this way is extremely unlikely, and this is an alert to a pathological state. The findings reflect a thrombo-occlusive state rather than an inflammatory-lytic state (bland infarcts without inflammation) which implies something about the underlying diagnosis. The differential is limited to just a few types of pathology: this could theoretically have happened due to severe aortic occlusive disease with lumbar ischemia (atheromas or aneurysm), but this patient had no macro-vascular disease, leaving the auto-immune connective tissue disorders and the various micro-occlusive disorders as possibilities. In this case, a specific diagnosis was not made beyond the rheumatoid itself, but laboratory profile showed markers of a hypercoagulable disorder or thrombotic state (high protein C and fibrinogen). Operative debridement of the wound (including coverage with a pathergy-controlling semi-biological material) triggered a profound hypo-coagulopathy, and the patient died shortly afterward from uncontrollable diffuse hemorrhage.

Figure 1 shows the midline lumbar wound as it appeared 1-2 weeks after surgery. The appearance is notable both for what is there, and what is

not. What is not there: no gross inflammatory changes, no signs of suppuration nor suppurative necrosis, no significant edema and no scarlet erythema in the peri-wound. What is there: cyanotic vascular stasis and skin infarcts at the wound margins, and infarcted bones, muscles, and fascias. Note the piece of gelatin sponge (left edge) used to stop some troublesome bleeding. This case reiterates that when the complex coagulation system becomes acutely pathological and dynamically unbalanced, then hyper- and hypo-coagulable events can occur concurrently (see case #3).



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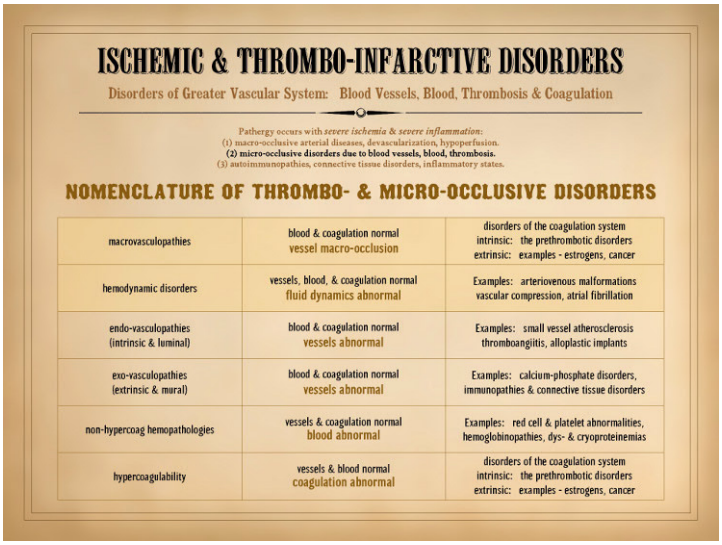
Case #07
(Set 2, pathergy & pathological wound complications)
Another case illustrating wound pathergy and serious patient risk.

This 58 year old man had coronary angioplasty, seemingly uncomplicated until a week or two after starting warfarin. Diffuse multifocal skin infarcts occurred involving many anatomical areas. The right lower extremity required amputation, which was complicated by skin infarcts along the edges of the incisions. Across his body, debridement, open wound management, and interim closure with semi-biological matrices were all complicated by progressive infarcts. While unusually severe, this was otherwise a typical case of warfarin necrosis. It generally occurs within the introductory few weeks of warfarin anticoagulation, attributed to ungoverned relative imbalances between the vitamin K dependent clotting factors as these proteins go from their normal to their therapeutic low levels. This complication is more apt to occur in someone whose coagulation system is already "untuned" due to a prethrombotic hypercoagulopathy, and for this patient, laboratory evaluation confirmed APC resistance (activated protein C), implying a factor V mutation. (For at-risk patients with an existing hypercoagulopathy, this complication can be prevented by concurrent treatment with heparins until warfarin effects are therapeutic.) The patient died from multi-system failure due to visceral infarcts. Wound pathergy can have a spectrum of severity, from self-limited and anatomically confined (such as a small lesion of pyoderma gangrenosum), through disastrous outcomes like this one. As a generic concept, its significance and risk to the patient cannot be trivialized.

Figures 1, 2 show the vascular stasis and multifocal infarcts on the trunk and extremities. Note the thrombo-infarctive appearance of the tissues, with stasis and cyanosis, but no edema or other gross inflammatory changes. **Figure 3** shows the right thigh after amputation and debridement. The ilio-femoral and tibio-peroneal vessels were all patent at the time of amputation, consistent with the micro-occlusive nature of the problem. Necrosis is present at the margins of incisions and sutures – this is wound pathergy. **Figure 4** is a closeup of some of these pathergic changes. Plastic surgeons will all be familiar with these findings, common events along the margins of any incompletely vascularized flap. The principles of good "flapology" are meant to avoid, mitigate, or manage these problems. The situation illustrated was unexpected, and the underlying cause and its complications were fatal, but it is nonetheless identical to the ischemic flap, an issue of critical soft tissue hypoperfusion in which any further insult or injury can cause necrosis.



28
Micro-occlusive, ischemic, and thrombo-infarctive disorders

Now that the concept of pathergy has been introduced, it is time to look at specific primary disorders that can lead to wound pathergy and failure. We will start with the ischemic and thrombo-infarctive disorders. The focus here is not so much on those that cause incidental large vessel obstruction and infarcts, such as athero-sclerosis causing myocardial infarction and strokes, but rather those that cause a perpetuated or "sustainable" form of ongoing micro-vascular occlusion with ongoing micro-thrombosis and inflammation.

Remember, wound pathergy occurs in association with conditions of severe ischemia & severe inflammation. From a clinical point of view, these can be divided into three pragmatic categories of disease: (1) macro-occlusive arterial diseases, devascularization, and hypoperfusion; (2) micro-occlusive states due to disorders of blood vessels, blood elements, and thrombosis; (3) autoimmunopathies, connective tissue disorders, and inflammatory states. This slide presents a simple nomenclature for the second category, micro-occlusive disorders causing thrombo-infarction and ischemia.

The ischemic, micro-occlusive, and thrombo-infarctive disorders are those that plug up blood vessels and thereby arrest the circulation to greater or lesser volumes of tissue. At face value, these are disorders of the greater vascular system and all of its components, the blood vessels, the blood itself, and the thrombotic system. There are many categorical types of primary pathology that can lead to these vascular and blood disorders – genetic and familial disorders (e.g. factor V Leiden), ageing and degenerative diseases (atherosclerosis), metabolic disorders

(e.g. hyperparathyroidism), neoplastic diseases (e.g. leukemias), immune and inflammatory states (e.g. lupus), pharmacological effects (e.g. estrogens), and others. Regardless of the multitude of primary pathologies that can lead to these states, their pathological effects on the greater circulation and its components can be reduced to a sensible nomenclature that can guide analysis and treatment planning for these disorders and their complications and sequelae. Thrombotic and micro-occlusive disorders can be grouped in five main categories.

1 – Hemodynamic disorders: Conditions of altered blood flow mechanics. Thrombosis occurs from blood stasis due to the hemodynamic alterations. These are usually related to gross cardiovascular anatomy and function (e.g. atrial fibrillation, valvular pathology, vascular compression). Blood vessels, blood, and coagulation are all intrinsically normal.

2 – Endovasculopathies: Blood vessels are abnormal due to intrinsic and luminal vasculopathies. Thrombosis occurs in response to blood stasis or thrombotic activation created by endoluminal and endothelial alterations in the vessels (e.g. atherosclerosis, hyperparathyroidism-calciphylaxis). Blood as a whole and the coagulation system are both intrinsically normal.

3 – Exovasculopathies: Blood vessels are abnormal due to extrinsic and mural vasculopathies. Unlike the endovasculopathies in which thrombosis is triggered by thrombogenic surfaces and flow turbulence or stasis, the exovasculopathies tend to be inflammatory or immune in origin, with inflammatory mediators triggering thrombosis in passing blood (e.g. venous vasculitis, the connective tissue disorders, and classic arteritides such as polyarteritis nodosa and thromboangiitis obliterans). Blood and the coagulation system are both intrinsically normal.

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 - red cell, leukocyte, & platelet abnormalities, 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 "pre-thrombotic" primary disorders of the coagulation system) or extrinsic due to metabolic or auto-immune alterations.

Perhaps not so much for group 1, the hemodynamic disorders, but all others are major causes of wound pathergy, surgical complications, impaired wound healing, and chronic ulceration. The vasculopathies and hemopathologies are generally well known and appreciated in general medicine. It seems though that the hypercoagulable disorders are not so well appreciated, despite their prevalence and profound ability to create human pathology. Thus, they get some extra attention in the next few paragraphs.

Recall the function of thrombosis – 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. 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 thus be acute and overt. They also commonly involve small vessels, and when they do, the clinical problems tend to be subtle, occult, persistent, and hard to recognize or treat.

All physicians have some familiarity with the thrombosis system when it is untuned toward a hypocoagulable state. The risk is for excessive or uncontrollable bleeding, hemorrhagic events triggered or exacerbated by trauma, sepsis, factor deficiencies, marrow suppression, anticoagulant drug effects, etc. However, 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 sequelae and clinical presentations. "Old medicine syndromes" due to large vessel macro-thrombosis, such a coronary or cerebrovascular occlusion, femoro-popliteal embolism, pulmonary embolism, and Budd-Chiari hepatic thrombosis are overt, dramatic, and easy to recognize. Small vessel micro-thrombosis tends to be subtle, ongoing, frustrating, and easy to overlook, misinterpret, or misdiagnosis.

Hypercoagulable states can be recognized by syndromic features. The clinical syndrome of occult hypercoagulopathy is a dependable tetrad or pentad of features, and if on history alone your wound patient has these things (only 2 or 3 need be present), then they have a hypercoagulable disorder: **1** – history of thrombotic or embolic events; **2** – history of miscarriages; **3** – history of wound pathergy (unexpected wound complications following trauma or surgery) or soft tissue problems including chronic ulceration; **4** – an auto-immune or connective tissue disorder; & **5** – (what makes it the pentad) a family history of the main 4 counts equally as a positive personal history. If the laboratory can confirm the diagnosis by positive identification of a hypercoagulable chemical, so much the better, but the diagnosis of a hypercoagulable state can reliably be made based on this syndromic clinical tetrad-pentad.

Returning to the general subject of the thrombo-infarctive disorders, following are three sets of illustrative cases showing wounds, pathergy, and surgical complications from micro-occlusive vasculopathies, hematopathologies, and hypercoagulopathies. Remember though that thrombosis, pathergy, and their complications are often due to more than just the overt or nominal primary diagnosis or risk factor. Wound pathergy is often not so simple as just a single thrombotic or embolic occlusive event, nor of a single inflammatory focus, etc. It is a consequence of interplay between thrombosis, inflammation, and necrosis-ulceration, that complex auto-amplifying set of events that leads to disintegration of orderly physiology and potentially catastrophic tissue destruction.

Further information on the subjects of micro-occlusive disorders, hypercoagulability, and related clinical syndromes and care are at:

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_annotated.pdf
(Not) Atypical Wounds
http://www.arimedica.com/content/arimedica_(not)%20atypical%20wounds_gottlieb-me_2009-0926_annotated.pdf
Hypercoagulability – Prethrombotic and Microthrombotic Disorders.
http://www.arimedica.com/content/arimedica_hypercoagulable_annotated_(pages)_2005-1027.pdf
Coagulopathic Ulcers – Criteria and Nomenclature.
http://www.arimedica.com/content/arimedica_hypercoagulable_(poster)_2006-0516.pdf

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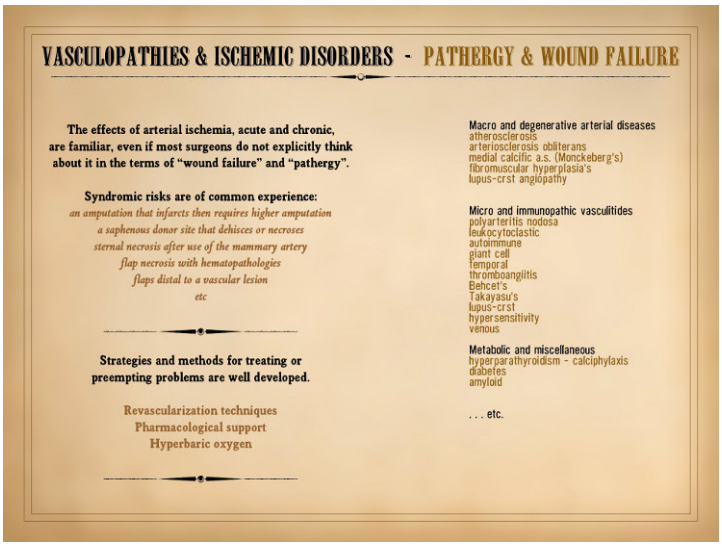
Set 3: Necrosis, ulceration, and wound pathergy:
Micro-occlusive vasculopathies

This is the first of three sets of illustrative cases that demonstrate the problems due to micro-occlusive ischemic disorders. The three sets are grouped by vasculopathies, the non-hypercoagulable hematopathologies, and the hypercoagulopathies.

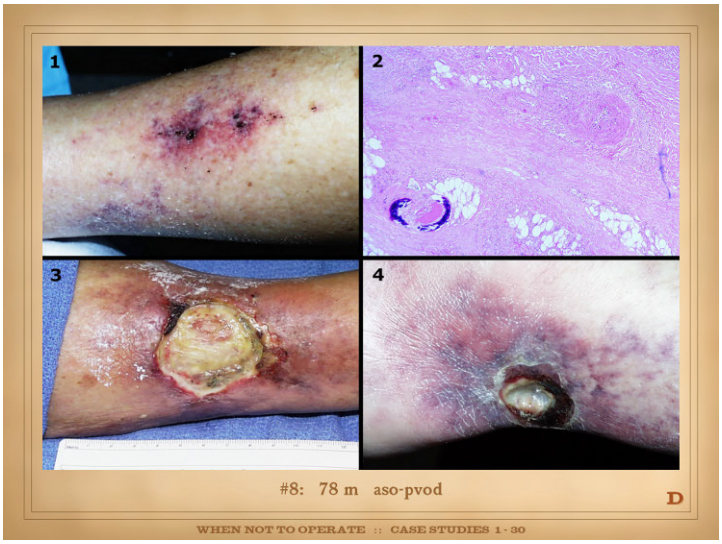


30
Vasculopathies & ischemic disorders

Because of the prevalence of vascular disease, and the general level of experience and sophistication that medicine as a whole has with it, the effects of arterial ischemia are familiar to most physicians. Even if a physician does not think of those effects explicitly in terms of "wound failure" and "pathergy", most have witnessed such events, whether related to acute or to chronic conditions of arterial insufficiency. Consider common scenarios following surgery: a lower extremity amputation that infarcts then requires higher amputation; a saphenous vein donor site (for coronary or other bypass) that dehisces or necroses; sternal necrosis after use of the mammary arteries (typically for coronary bypass); reconstructive flaps with a perfect pedicle nonetheless die because the pedicle is distal to an occlusive atheroma; technically correct flaps become necrotic in the face of thrombogenic hematopathologies.

Listed on the slide are some of the classic or well recognized clinical syndromes of macro- and micro-occlusive arteriopathy, grouped by pathological category. **Macro and degenerative arterial diseases:** atherosclerosis, arteriosclerosis obliterans, medial calcific arteriosclerosis (Monckeberg's), fibromuscular hyperplasia's, scleroderma-crst-lupus angiopathy. **Micro and immunopathic vasculitides:** polyarteritis nodosa, leukocytoclastic, autoimmune, giant cell, temporal, thromboangiitis, Behcet's, Takayasu's, lupus-crst, hypersensitivity, venous. **Metabolic and miscellaneous:** hyperparathyroidism – calciphylaxis, diabetes, amyloidosis, etc.

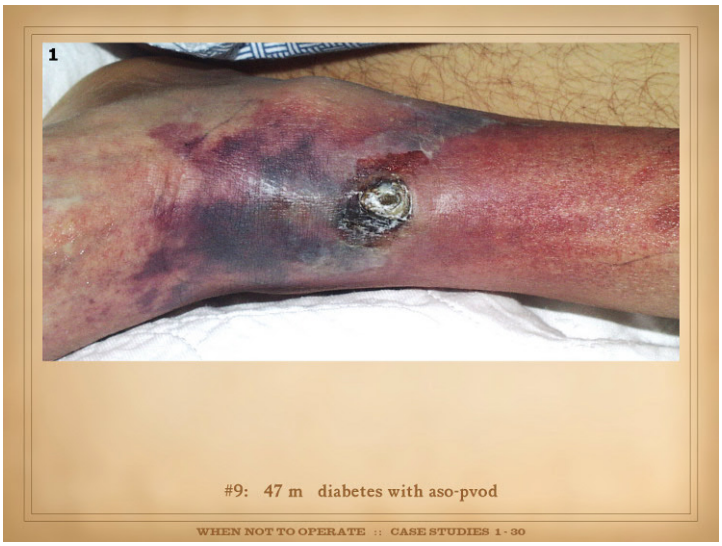
Because of the prevalence of vascular disease, and the general experience with it, the strategies and therapeutics for preventing or treating such problems are well developed. These include robust methods and technologies for surgical or procedural revascularization, pharmacological support, and hyperbaric oxygen. It is unfortunate when a vascular event, typically a macro-vascular thrombosis or infarct, occurs acutely to a major organ and so severely jeopardizes life that there might be no time to intercede and correct the problem. Fortunately though, for the many other arterio-occlusive disorders that can cause profound misery, they occur slowly or chronically, allowing ample opportunity to treat after an event, or to correct an underlying ongoing condition, or to preempt problems in advance of planned surgery or other care. With respect to the more subtle or subclinical disorders often due to micro-occlusive angiopathies, the biggest problem is in not being aware of their presence or not anticipating the trouble they can make when undertaking surgery. All surgeons must be ever vigilant about these disorders, to recognize their pathogenic role when confronted with a problem already occurred or in evolution, or to protect against complications in at-risk patient when planning or undertaking their surgery.



31
Case #08
(Set 3, micro-occlusive & ulcerogenic disorders: vasculopathies)
Illustrating wound pathergy due to atherosclerosis and arterial insufficiency.

This 78 year old man presented with skin infarcts and ulcers of the legs and ankles. He had ilio-femoral atherosclerosis associated with hypertension and hyperlipidemia. Although vascular reconstruction was attempted, arterial flows remained low. Histology of debrided material showed that atherosclerosis also involved small cutaneous vessels. Debridement was associated with progressive skin necrosis at wound margins. Leg amputation might have controlled symptoms but was also at high risk for wound pathergy and the need for high level or progressive amputation. Instead, the wounds and general functional status were maintained with hygienic topical care until the patient died from cardiovascular events unrelated to the leg.

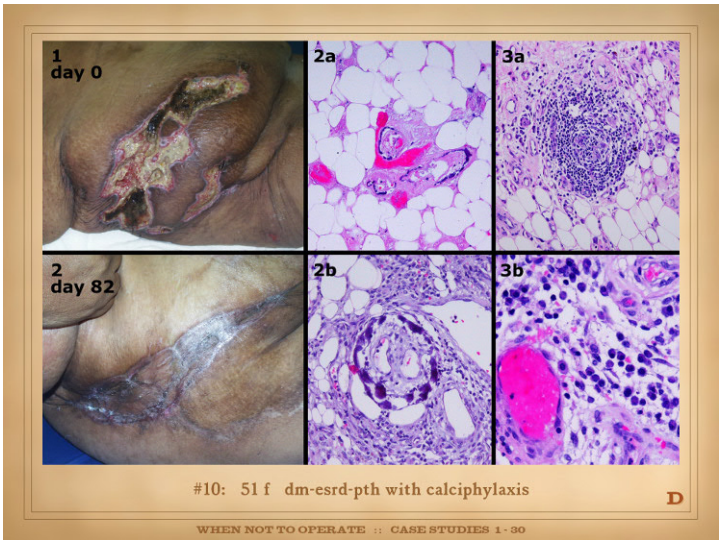
Figure 1 shows one of the several cutaneous infarcts that developed on the legs. **Figure 2** shows that dermal and hypodermal vessels are sclerotic and have reorganizing thrombus. Absent a risk profile or any laboratory markers of a hypercoagulable state, the thrombosis here is due to low flows from the altered small vessels, and heightened thrombogenicity of those pathological vessels. The debridement which supplied the specimens was subject to pathergy, as seen in **figure 3** (above the malleolus) and **figure 4** (over the achilles), which demonstrate progressive vascular stasis and wound margin necrosis after incision and debridement.



32
Case #09
(Set 3, micro-occlusive & ulcerogenic disorders: vasculopathies)
Another case illustrating wound pathergy due to atherosclerosis and arterial insufficiency.

This 47 year old man had diabetes, end stage renal disease, and atherosclerosis with high grade tibio-peroneal occlusion. He presented with urinary sepsis and intercurrent complications. The original anterior ankle ulcer was pre-existing, probably from some mundane trauma, a small bruise or laceration, something presumably innocuous had it been in a normal person. As acute illness progressed, skin infarction and signs of profound arterial stasis ensued, progressing outward from the original ulcer. This is a dominant feature of ischemic wound pathergy. Any focus of injured tissue, thrombosis, inflammation, or interrupted flow patterns, including surgical incisions, becomes the hub from which develops more of the same. Any number of hemodynamic, coagulopathic, and inflammatory events can trigger progression of the infarcts, and so too can treatment, including pressure from bandaging and any sort of further trauma such as biopsies, debridement, or any other surgery. (After transfer to another facility, outcome is unknown.)

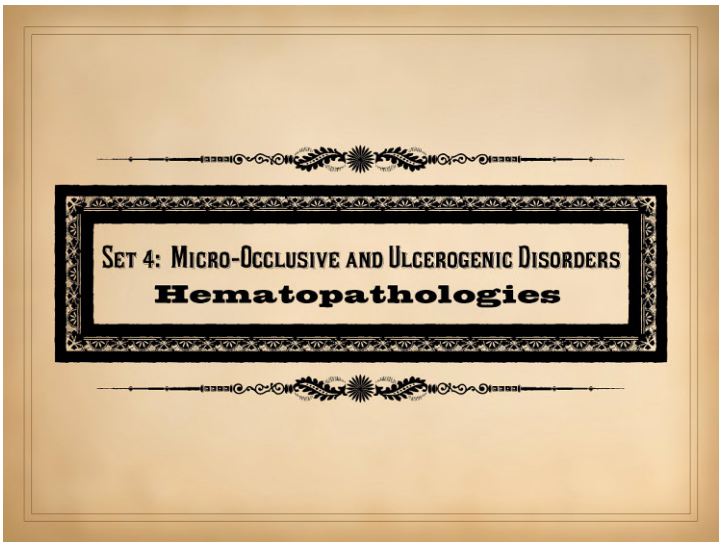
Figure 1 shows the prior ankle ulcer, now infarcted and escharotic after onset of generalized illness. This is apt to happen in a patient with vascular disease and low flows who then develops a state of injury-inflammation-thrombosis or hemodynamic alterations such as hypotension. The problem is exacerbated in a patient who has a pathergy prone hematopathology such as thrombocytosis. The magenta and violet discolored areas represent areas of extreme low flow and arterial stasis, leading to regional thrombosis and extension of the infarct. Any incision into these tissues, which will correctly trigger local thrombosis and inflammation, will do more of the same. Unless the foot and leg can be revascularized, amputation is probably unavoidable. In the 1960's and 1970's, vascular surgeons taught us that arteriopathic legs need not be indiscriminately amputated, that revascularization will recover the situation. That concept of "limb salvage" is true, but not sufficient. Skin, wounds, and incisions must be managed as well. For discussion's sake, assume that this particular patient had good circulation at thigh level, and that although below-knee amputation might be of questionable outcome, an above-knee amputation would be certain to heal. Today's concepts and technologies mean that preemptive management of pathergy risks, utilizing the many applicable therapies in support of the "cut-and-sew" procedure, should allow for successful amputation at a level distal to the certain "no problem" level, making below-knee amputation feasible for this patient.



33
Case #10
(Set 3, micro-occlusive & ulcerogenic disorders: vasculopathies)
Illustrating wound pathergy due to micro-atherosclerosis.

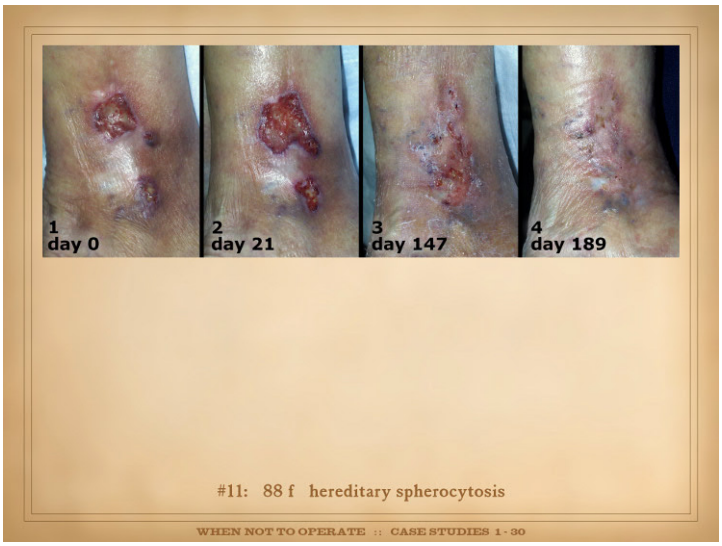
This 51 year old woman, with diabetes and end stage renal disease, presented with painful infarcts of skin and subcutaneous fascias on the abdomen and breast. The presentation, history, and features of the lesions were pathognomonic of calciphylaxis, confirmed by histology (showing calcific micro-arteriosclerosis and micro-thrombosis), and further supported by high parathormone levels and low transcutaneous oxygen levels. Characteristically in this ischemic disorder, tissues tend to heal very slowly when treated by topical care in support of natural contraction. Skin grafts typically are uncertain, and direct repair and local flaps tend to fail. Likewise, simple debridements and biopsies also risk progression of the infarcts and wounds, just as for any micro-thrombotic or ischemic tissue. This patient had successful and rapid resolution of the lesions by using a pathergy-preventing protocol: complete excision, immediate closure with a semi-biological regenerative matrix (Integra™), and short term support of potential post-operative wound ischemia with hyperbaric oxygen.

Figure 1 shows the skin and pannicular infarcts on the right flank and abdomen. Similar lesions were on the left side and on the breasts. **Figure 2** shows the completed reconstruction, completely healed and maturing 3 months later. The skin and pannicular lesions of hyperparathyroidism-calciphylaxis are often viewed as highly morbid and difficult to treat, but that perception is illusory. This is a benign form of micro-occlusion, without intrinsic or primary inflammatory events, and without intrinsic wound healing deficits (unlike the auto-immunopathies and connective tissue disorders in which wound healing is intrinsically damaged). If microperfusion and oxygenation can be maintained, and if peri-operative pathergy can be prevented, these lesions heal quite easily. **Figures 2a, b** show the primary pathology of this disorder, small vessel calcific arteriosclerosis. However, it is not the calcium deposits which kill tissue, it is the secondary thrombosis, seen here in later phases of organization and recanalization. **Figures 3a, b** show a chronic peri-arteritis around vessels which are occluded or congested. As in any chronic inflammation, lymphocytes and plasma cells predominate. Neutrophils and a generalized inflammatory process in surrounding tissues are absent. While hyperparathyroidism and calcific arteriopathy might be the nominal pathology of this disorder, the reality is that pathergy-prone disorders and soft tissue infarcts generally represent a complex interaction of injury-thrombosis-inflammation which can be triggered in many ways. Remember that the micro-occlusive disorders tend to be subtle, insidious, and ongoing . They can have a multitude of "soft" and non-specific symptoms and thereby elude timely recognition or diagnosis. The ongoing and longstanding micro-infarcts that they cause are the basis for eventual late phase lymphoid recognition and auto-immunization, as confirmed by these perivascular lymphoid deposits. In this patient, and in all the other patients with this diagnosis, recognizing and appreciating the primary pathology and then the secondary pathogenesis of infarction and wound pathergy allows these risks and events to be managed and treated with predictably good results.



34
Set4: Necrosis, ulceration, and wound pathergy:
Micro-occlusive hematopathologies

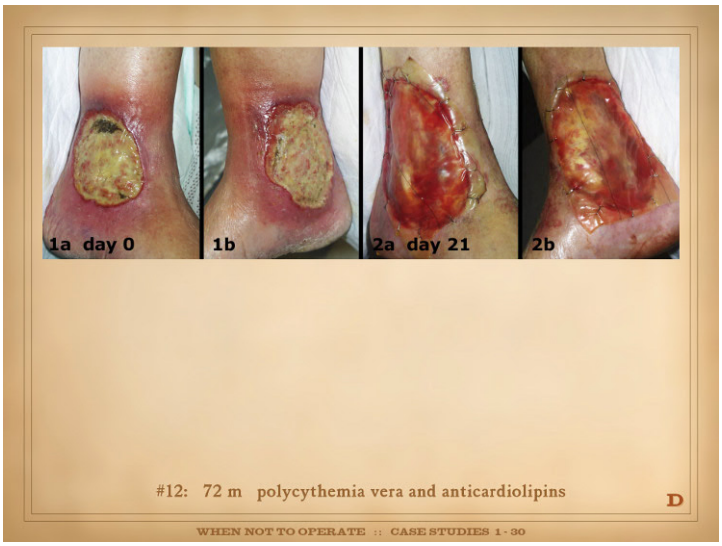
This is the second of three sets of illustrative cases that demonstrate the problems due to micro-occlusive ischemic disorders. The three sets are grouped by vasculopathies, the non-hypercoagulable hematopathologies, and the hypercoagulopathies.



35
Case #11
(Set 4, micro-occlusive & ulcerogenic disorders: hematopathologies)
Illustrating wounds and risks due to red blood cell disorders.

This 88 year old woman had multifocal ankle ulcers characteristic of immune and hematological diseases. There were no stigmata of venous disease, and arterial circulation was normal. She had hereditary spherocytosis (including chronic mild anemia and hyperbilirubinemia) not requiring therapy. She also had a history of rheumatoid arthritis, not currently active or treated. Laboratory evaluation showed numerous direct and indirect markers of a hypercoagulable disorder, including high fibrinogen, high protein C, hyperhomocysteinemia, and an unmeasurably high anticardiolipin. All of the hemoglobinopathies and hemolytic anemias carry the risk of chronic ulceration, but in this case, spherocytosis by itself was certainly not the only cause of the ulcers. Many patients with pathological wounds, both acute pathergy and chronic ulceration, will have markers of mixed and concurrent immune and hematological diseases. It is important to understand that nominal diagnoses such as "spherocytosis" or "primary thrombocytosis" cannot be accepted at face value as the cause of severe wound and soft tissue complications. This patient healed with topical care and warfarin anticoagulation over a period of 6 months. Any attempt to solve the problem with basic wound repairs or local flaps would have simply made the problem worse.

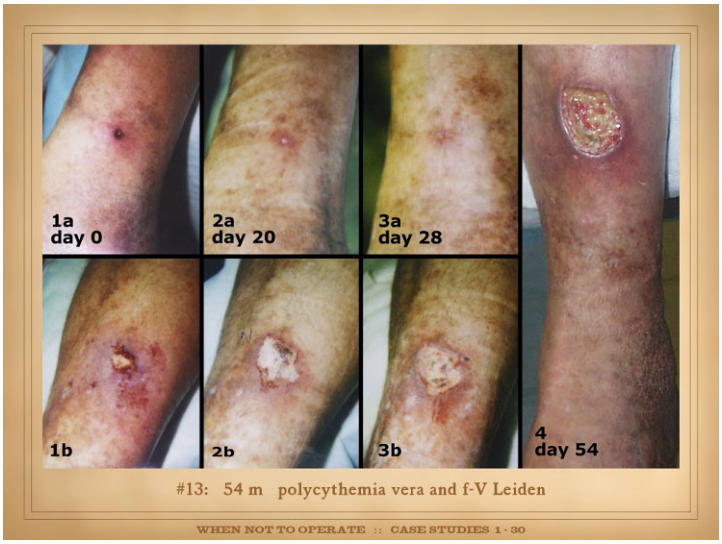
Figure 1 shows the left lateral malleolus and ankle at presentation. **Figure 2** (day 21) shows that the original foci enlarged and coalesced over 3 weeks. During that interval, the wounds were kept clean by basic care, but no diagnosis-specific therapy was started while awaiting the laboratory evaluation mentioned above. Warfarin therapy was then started, and the wounds began to heal. Epithelial growth was slow but consistent, and the wound was healed then stable 4-5 months later (**figures 3, 4**, day 147 & day 189).



36
Case #12
(Set 4, micro-occlusive & ulcerogenic disorders: hematopathologies)
Illustrating wounds and risks due to hypercythemias and polycythemias.

This 72 year old woman had polycythemia vera. Her blood counts broke through therapy, and she developed multiple ankle ulcers. At the time of consultation, while otherwise healthy and non-acute, her red blood cells were normal, but white blood cells were 35K/mm3 and platelets were 760/mm3. Workup for associated disorders was significant for positive anti-nuclear antigens (1:160), elevated rheumatoid factor, low protein C, and high anticardiolipins. The patient was started on warfarin, the leg ulcers were prepared by basic topical care, and then skin reconstruction was started with Integra™ collagen-gag regenerative matrix. The reconstruction was never completed because the patient died from an acute cerebro-vascular occlusion and infarct. The ulcers are prototypical pathological wounds due to immune or hematological disease. Such lesions on the distal leg and ankle can have several distinctive modes of onset: random panniculitis, dermatitis, or vasculitis; immune synovitis along tendons and bursas; or due to minor trauma (wound pathergy). Trauma-pathergy (starting as everyday bumps and dings on the ankle) and immune bursitis are the common modes for initiating malleolar ulcers. Note that although she had a nominal diagnosis of a myeloproliferative disorder, she had significant markers of immunopathy and coagulopathy, a very common association, illustrating again that a major wound complication cannot be blithely attributed solely to "benign thrombocytosis".

Figure 1 shows the right ankle and ulcers (1a is lateral, 1b is medial). There is active necrosis and ulceration at the margins, and the periwound has vascular stasis and intense inflammation. The pattern is mainly inflammatory-lytic rather than thrombo-infarctive, consistent with auto-immunity rather than micro-occlusion being the primary pathology. This illustrates the principle that simple assumptions about diagnosis and pathogenesis, such as "sludging from high platelet counts", are naive and inconsistent with the information that can be gleaned from a proper history, exam, and laboratory investigation. **Figure 2** shows the same views 3 weeks later, after excising the wounds and closing them with Integra™ collagen-gag regenerative matrix. Note the complete control of periwound inflammation and active ulceration. In a patient like this, simple cut-and-sew surgery without regard to controlling pathergy will be subject to continued inflammation and wound failure.



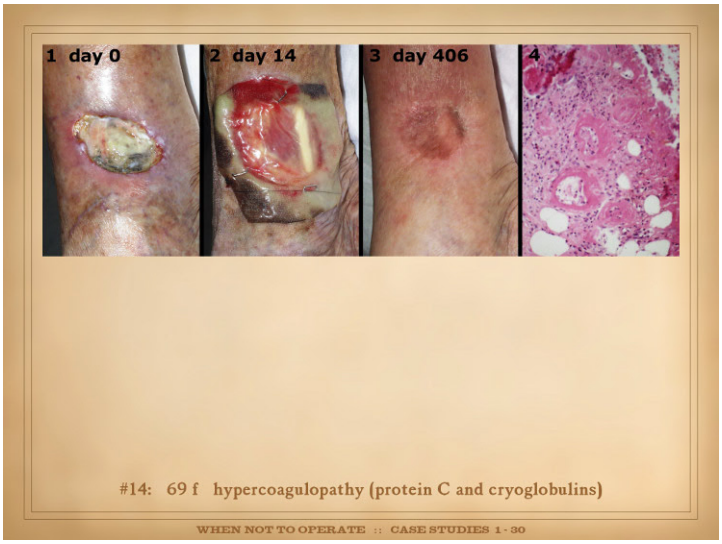
37
Case #13
(Set 4, micro-occlusive & ulcerogenic disorders: hematopathologies)
Another case illustrating wounds and risks due to polycythemias and mixed hematological disease.

This 54 year old man had multifocal leg ulcers characteristic of immune and hematological diseases (with no signs of venous disease or arterial insufficiency). He had polycythemia vera, counts well controlled with treatment, and a history of venous thrombosis and pulmonary embolism. Laboratory evaluation showed numerous direct and indirect markers of a hypercoagulable disorder, including high fibrinogen, low proteins C & S, hyperhomocysteinemia, a lupus anticoagulant, unmeasurably high anticardiolipins, elevated speckled anti-nuclear antibodies, and factor V Leiden heterozygote. Polycythemia vera is a nominal risk for leg ulceration, but as in many patients with pathological wounds, markers of immune, hematocellular, and hypercoagulable diseases occur concurrently, making the problem much more complex than just the index diagnosis. This is very similar to the previous cases, and once again it is important to understand that the "face value" diagnosis cannot be accepted blindly as the only cause of wound and soft tissue complications. This patient healed with topical care and warfarin over a period of months. Had wound repair surgery been attempted, it likely would have resulted in flap necrosis and wound failure.

Figure 1a (day 0) shows a small skin infarct and ulcer just proximal to the left ankle. Similar lesions were also present on the medial side of the leg. **Figure 1b** is another infarct, more proximal on the leg over the tibia. The central ulcer where skin is already missing is surrounded by a zone of severe vascular ischemia and stasis. Those darkly colored zones are in the throes of necrosis or already necrotic. **Figure 2** shows the same lesions at 20 days. The small ankle lesion has stabilized with treatment. The pre-tibial lesion has also stabilized. It appears larger because the dark infarcted areas seen at day 0 have by now escharified and separated, but there are no signs of active new necrosis at the wound margins. **Figure 3** (day 28) shows the small lesion almost healed, and the larger lesion showing early signs of wound proliferation. This is not robust normal healing, but the periwound is free of inflammatory changes, and no new ulceration is occurring. **Figure 4** (54 days) shows that minor lesions throughout the distal leg are healed, and edema and skin quality are generally improved. Wound healing kinetics of the large tibial ulcer remain obviously delayed, but they are qualitatively correct, and this wound is expected to heal with topical care and wound stimulatory therapies. (The patient also had multi-pathology heart disease; shortly after this he had heart catheterization, and subsequent status is unknown.)

38
Set5: Necrosis, ulceration, and wound pathergy:
Micro-occlusive hypercoagulopathies

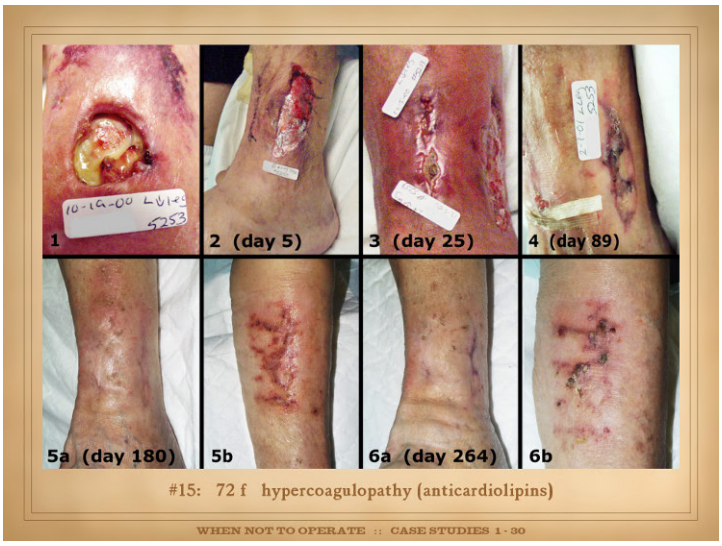
This is the third of three sets of illustrative cases that demonstrate the problems due to micro-occlusive ischemic disorders. The three sets are grouped by vasculopathies, the non-hypercoagulable hematopathologies, and the hypercoagulopathies.



39
Case #14
(Set 5, micro-occlusive & ulcerogenic disorders: hypercoagulopathies)
Illustrating wounds and pathergy due to a hypercoagulable disorder.

This 69 year old woman had biopsy of a small lesion on the leg. She had no relevant medical history, and pulses were normal. The small sutured biopsy site promptly became ulcerated, and a proliferative wound module failed to appear after a period of basic topical care. Laboratory evaluation confirmed a hypercoagulopathic or micro-occlusive state from cryoglobulins and protein C deficiency. Warfarin was initiated, and then skin was successfully reconstructed with a pathergy preventing regenerative material (Integra™ collagen-gag matrix). Conventional cut-and-sew surgery, had it been attempted without prior anticoagulation, would have resulted in the same kind of pathergy and wound failure as accompanied the original biopsy, merely making the problem bigger (see case #24).

Figure 1 shows the ulcer on the right medial ankle, the result of a seemingly innocuous skin biopsy for a non-ulcerated lesion suspected of being an epithelioma. There is active ulceration at some of the margins, necrosis along the base of the wound, and absence of significant periwound inflammation. This is the thrombo-infarctive pattern of necrosis and ulceration, consistent with primary micro-thrombosis. **Figure 4** histology confirms necrosis at the ulcer base, along with vascular thrombosis and necrosis of the vessels themselves, without dense or neutrophilic inflammation, a typical histology of hypercoagulable ulceration. **Figure 2** shows the wound after excision and closure with a pathergy controlling material. Wound colors are healthy, and there is no new necrosis. **Figure 3** is the healed and stable wound a year later. The ulcer itself was the pathergic response to excision of a small skin lesion, so any attempt to do further debridement or conventional surgery without controlling this pathological response would simply have enlarged the entire problem.



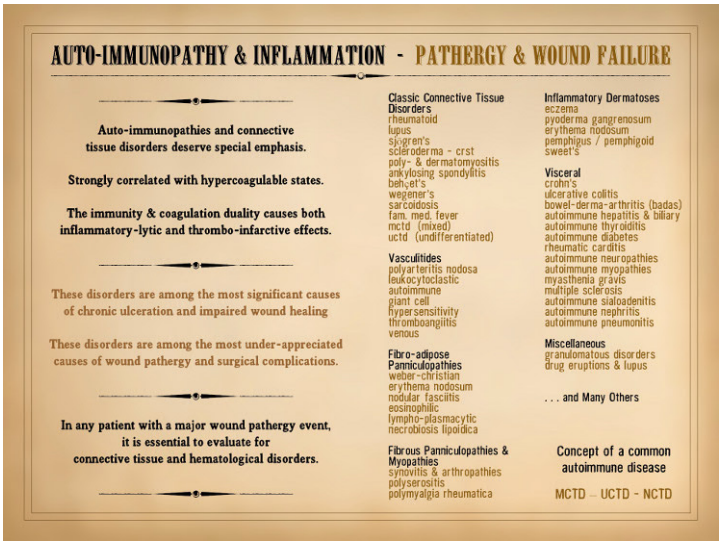
40
Case #15
(Set 5, micro-occlusive & ulcerogenic disorders: hypercoagulopathies)
Illustrating wounds and pathergy due to a hypercoagulable disorder.

This 72 year old woman had a minor household injury, bumping the leg against furniture, causing a small wound which became progressively and chronically ulcerated. The patient gave no history suggestive of immune or hematological disorders, and arterial exam was normal. Exposure of gliding muscle in the anterior compartment required a small flap for closure. Assuming this to be a benign wound due solely to trauma, closure was done with a local flap, and the flap donor site was closed with a skin graft. The flap appeared well vascularized in surgery, and it did survive and eventually heal. However, it went through a period of unexpected relative ischemia, and complete healing was delayed by recurrent areas of necrosis and ulceration at its margins The skin grafts placed on the flap donor site immediately became necrotic, but that site too healed eventually. Well after the primary reconstruction was healed, the thin split thickness skin graft donor site remained unhealed with signs of vascular stasis and recurrent small infarcts and ulcers. Curiosity about the cause of these variances from expected behavior prompted a laboratory screen for immune and coagulopathic disorders, and they were positive, a primary elevation of anticardiolipins with a reflex elevation of protein C. Anticoagulation was not started because by then everything was healed. Had the patient had a suggestive history before surgery, anticoagulation would have been started at the beginning, and the delayed healing would have been avoided. This story of unexpected ulceration after minor trauma, the failure of incisions and grafts, infarcts along incised edges, and delayed healing all illustrate, indeed epitomize, the definition and nature of wound pathergy, and they are all manifestations of the underlying disease that caused it.

Figure 1 is the original ulcer of the anterior left leg prior to surgery. The skin margins and subcutaneous fascias have areas of active infarction and ulceration, a tipoff to active pathology. **Figure 2** is the reconstruction, a bipedicle flap, 5 days after surgery. While some ischemia could occur in a bipedicle flap, the area of cyanosis was inconsistent with the healthy appearance and bleeding during surgery. Note too the loss of the skin graft. The suture line, i.e. the coapted edges of the excised ulcer is healthy. **Figure 3** (25 days) shows small ulcers and eschar at the coapted edges, occurring on both the flap and the static margins (i.e. not just due to flap ischemia). At 3 months (**figure 4**) the reconstruction is still not fully healed. It is healed at 6 months (**figure 5a**), and remains so at 9 months (**figure 6a**). However, at the same times, the skin graft donor site has persistent vascular stasis with small infarcts and ulcers (**figures 5a, 6b**).

41
Set 6: Immune disorders and wound pathergy

This set of cases illustrates wound pathergy, wound failure, and clinical morbidity and complications due to disorders of heightened inflammation, immunity, and auto-immunity.



42
Auto-immunity & inflammation causing pathergy & wound failure

With respect to wounds and wound failure, the auto-immunopathies and collagen-vascular diseases deserve special emphasis. These connective tissue disorders are among the most significant causes of chronic ulceration and impaired wound healing. For reasons beyond the scope of this discussion, the converse is also true. Not only do the cvd-ctd's cause wounds, the chronic impaired wound is in essence a collagen-vascular connective tissue disorder. Also, aside from their core immune alterations, they can cause or be associated with vasculopathies and hypercoagulopathies. Any associated problem wound can thus have multifactorial causes of ulceration or wound healing failure. The immunity-ischemia duality of many of these wounds is appreciated on exam because inflammatory-lytic and thrombo-infarctive features are often both strongly evident. Furthermore, these disorders are among the most under-appreciated causes of wound pathergy and surgical complications. As such, these wounds are often the most refractory and difficult to heal among all comers to a wound care practice.

In any patient with a major wound pathergy event, it is essential to evaluate for connective tissue and hematological disorders.
Listed on the slide are some of the classic or well recognized clinical syndromes or nosological entities that fall under the umbrella of the auto-immune disorders. They include the following, grouped by pathological category. **Classic connective tissue disorders:** rheumatoid, lupus, Sjögren's, scleroderma - crst, poly- & dermatomyositis, ankylosing spondylitis, Behçet's, Wegener's, sarcoidosis, familial mediterranean fever, mctd (mixed ctd) , uctd (undifferentiated ctd). **Vasculitides:** polyarteritis nodosa, leukocytoclastic, autoimmune, giant cell, hypersensitivity, thromboangiitis, venous. **Fibro-adipose panniculopathies:** Weber-Christian, erythema nodosum, nodular fasciitis, eosinophilic, lympho-plasmacytic, necrobiosis lipoidica. **Fibrous panniculopathies & myopathies:** synovitis & arthropathies, polyserositis, polymyalgia rheumatica. **Inflammatory dermatoses:** eczema, pyoderma gangrenosum, erythema nodosum, pemphigus / pemphigoid, Sweet's. **Visceral:** Crohn's, ulcerative colitis, bowel-derma-arthritis (badas), autoimmune hepatitis & biliary, autoimmune thyroiditis, autoimmune diabetes, rheumatic carditis, autoimmune neuropathies, autoimmune myopathies, myasthenia gravis, multiple sclerosis, autoimmune sialoadenitis, autoimmune nephritis, autoimmune pneumonitis. **Miscellaneous:** granulomatous disorders, drug eruptions & drug induced lupus

. . . and Many Others. To reiterate, the autoimmune inflammatory collagen-vascular connective tissue disorders are potent causes of pathological ulceration, wound pathergy, and wound healing failure. Detailed information on these subjects is at **www.arimedica.com**, at:

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_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_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_annotated.pdf
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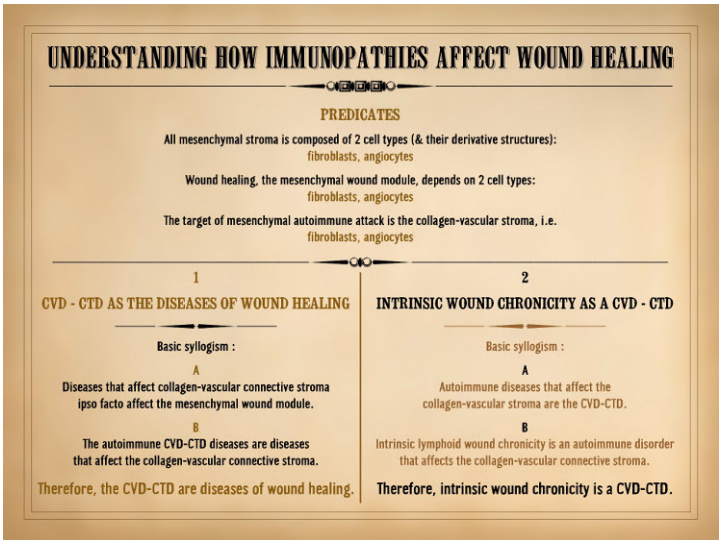


43
Understanding how immunopathies affect wound healing

Many wound healing problems are due to factors extrinsic to the core elements of the wound healing "machinery". The prototype example is vascular disease. Arterial insufficiency contributes to the occurrence of wounds. It causes wound pathergy. It retards wound healing kinetics and delays closure. But this is an adverse factor imposed on the wound by pathology extrinsic to the injured tissue. Regardless the clinical difficulties in a given situation, once circulation is restored to that area, wound healing dynamics return to normal. In contrast, the collagen-vascular connective tissue disorders are the true intrinsic diseases of wound healing. When they are active, the core elements of the "healing process", stromal repair due to angiocytes and fibroblasts, becomes dynamically deranged. Fundamental wound healing is broken, which is why these wounds can be so refractory to care and hard to heal.

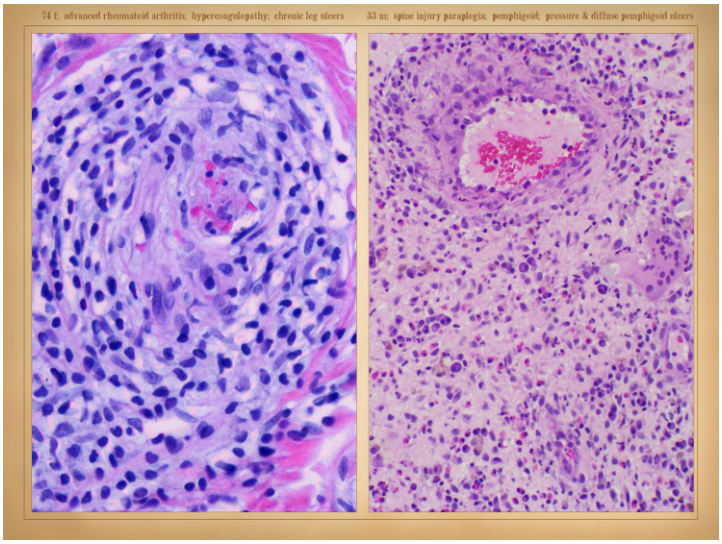
The detailed explanation for this can be read at the links on the preceding slide. However, since this issue is so central to the concept of wound pathergy, unexpected wound complications, and complications in surgery, it deserves reiteration. To state the connection between autoimmunity, connective tissue disorders, and pathological wound healing, we must start with three axiomatic predicates. **(1)** All mesenchymal stroma is composed of 2 cell types and their derivative structures: fibroblasts and angiocytes, blood vessels and connective matrix. **(2)** Wound healing, the proliferative mesenchymal wound module, depends on 2 cell types: fibroblasts and angiocytes, to remake vessels and matrix. **(3)** The target of mesenchymal autoimmune attack is the collagen-vascular stroma, i.e. fibroblasts and angiocytes, blood vessels and connective matrix.

Assertion 1: The collagen vascular connective tissue disorders are a disease of wound healing.
Basic syllogism :
A - Diseases that affect the collagen-vascular connective stroma ipso facto affect the mesenchymal wound module.
B - The autoimmune CVD-CTD's are diseases that affect the collagen-vascular connective stroma.
Conclusion: Therefore, the CVD-CTD's are diseases of wound healing.

Assertion 2: Intrinsic wound chronicity is a collagen-vascular connective tissue disorder.
Basic syllogism :
A - Autoimmune diseases that affect the collagen-vascular stroma are the CVD-CTD's.
B - Intrinsic lymphoid wound chronicity is an autoimmune disorder that affects the collagen-vascular connective stroma.
Conclusion: Therefore, intrinsic wound chronicity is a CVD-CTD.

These principles are not relevant to simple acute healthy wounds. However, the tissues that are the targets of collagen-vascular diseases are the tissues that heal a wound, so when auto-immunopathy is present, wounds may not heal. That is when wound pathergy is a risk or is manifest. These problems occur under two scenarios. **(1)** A wound occurs in the face of a prior or established connective tissue disorder. The wound and the disease are a coincidence. If the wound fails, the cvd-ctd is likely to have been a contributing factor. **(2)** The local tissues have become intrinsically auto-immunized, infiltrated by lymphocytes and plasma cells, a consequence of repetitive or sustained trauma and inflammation. This can occur for several reasons, including the "too much too soon too often" scenarios. Compared to other diagnoses or wound origins, the auto-immunopathic wounds have a particularly perverse and pernicious duality of effects: **(1)** they have an afferent effect to cause necrosis and ulceration, and then **(2)** they have an efferent effect to continue injuring or inhibiting the wound thus preventing healing. These disorders make the wounds, then they keep them from healing. These effects continue even after the wound is nominally healed, leading sometimes to chronic or intermittent cicatritis, localized panniculitis, and recurrent scar ulcers (a problem most apt to be seen with lupus and its close allies).

These disorders are demons lying in wait for the unwary surgeon. Or, they are demons bred by the imprudent surgeon who keeps operating when the wound demands time off or a vacation from more injury. A surgeon in pursuit of his "white whale" of closing a refractory wound is only making the problem worse, breeding and strengthening adverse cellular pathologies and histologies that assure failure and make the success of a closed wound ever harder to achieve. For more detailed information, read the articles referenced in the preceding slide.

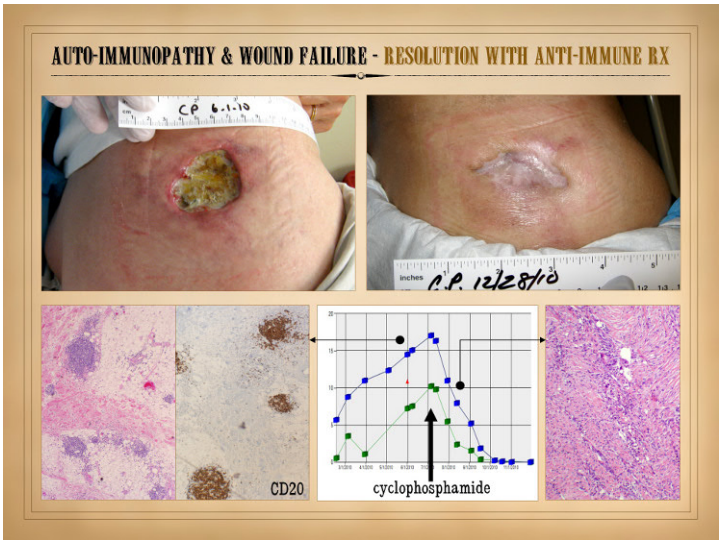


44
A view of how immunopathies affect wound healing

These two images demonstrate part of the cellular and biological basis for auto-immunization in wounds and why immunopathic wounds and those associated with cvd-ctd's can be so pernicious and refractory to care and healing. Both show that with the most refractory wounds are characterized by an abnormal infiltration of chronic (lymphoid) and mixed inflammatory cells that are never present in a healthy and properly healing wound. The origins of this aberrant inflammation is beyond the scope of this presentation, but details can reviewed at the links presented on Slide 11 and others.

Left, a 74 year old woman with a history of thrombotic events and overt crippling rheumatoid arthritis. She presented with multifocal leg ulcers, some randomly placed, some over tendon sheaths due to synovitis. There were distinctive thrombo-infarctive changes in some, inflammatory-lytic changes in others. These longstanding ulcers gradually healed completely with anti-coagulation, increased anti-inflammatory therapy, and skin reconstruction with regenerative matrices. Seen is a vascular locus without significant acute neutrophilic inflammation, nor are there poly's in the perivascular connective matrix. However, the vascular lumens are filled with acute and chronic thrombus including neutrophils. The vascular locus is hypertrophied, partly proper due to active wound healing angiogenesis, but partly improper due to infiltration with lymphocytes and plasmacytes. Something about the vascular locus is attracting or harboring the lymphoid cells. The attraction to angiocytes and vascular structures, especially those that are thrombosed would seem to imply some sort of auto-sensitization. While there could be more benign explanations for why the lymphocytes have taken up residence there, their immunogenic and defensive roles, and their consistent appearance around vessels in the most impaired wounds, strongly suggests that the lymphocytes are more likely cause rather than effect of the wound impairments.

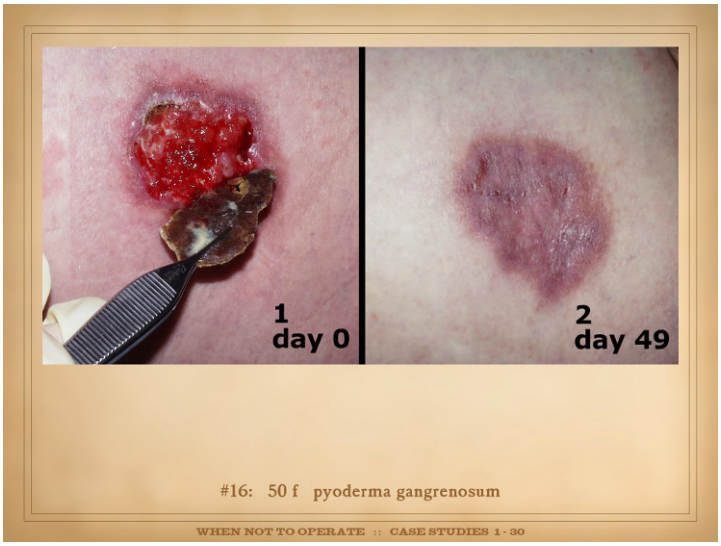
Right, a 33 year old man, who, after spine injury and paraplegia, developed diffuse chronic pathological ulcers. The lesions all began with initial blistering then persistent desquamation and failure to heal. The acute phase gross lesions and histology were consistent with an eosinophilic or allergic process, bullous pemphigoid being the "best fit" diagnosis. In the chronic phases, the gross and histologic appearances were more inherently chronic. The lesions improved with steroids, but ultimately healed only with azathioprine therapy. The primary "pathogen" in this situation was presumably some type of chemical exposure, e.g. therapeutic pharmaceuticals prescribed during his post-trauma hospitalization or else topicals related to wound care. What could have, should have, would have been an easy problem to treat if recognized and treated properly in the early phases became chronic and refractory to any standard wound therapy. Histology revealed the reasons why. This view is below the wound surface in what is nominally the angio-organization and histio-attraction strata of the wound. There is edema mixed with aminoglycans and scant if any collagen, yet there are large substantial vessels, either only semi-organized, or else disordered by persistent angioid activity and inflammatory infiltration. (Impaired, disorganized, aberrant, and failed wound strata are common findings in chronic and pathological wounds, especially autoimmune wounds.) The entire field is infiltrated with an intense mix of "everything", a CAP wound smorgasbord of all relevant cells which contribute to its sustained impaired pathological state. There are numerous neutrophils and some nuclear debris (in a healthy wound, poly's would be nearly absent from this stratum). There are monocytes-macrophages-histiocytes, present in reasonable numbers, but in a stratum deeper than where they would ordinarily appear. There are very active angiocytes, some coalesced into vessels, others breaking away, many migrating through the interstitial space, all morphologically typical of sustained wound healing dynamics resulting from active growth factors affecting the local responder cells. The normal separation of acute inflammation from wound module in time and space has failed, and these two populations are admixed, disrupting wound healing, and exposing potential antigen processing cells to increased amounts of debris and raw stromal detritus. Finally, the wound, both vessels and interstitium, is overrun with lymphocytes, plasma cells, and eosinophils. The eosinophils are consistent with the presumed allergic-atopic pemphigoid origin of the problem. The lympho-plasmacytes reveal a latter stage of immune sensitization. In this case, the chronic allergic state is probably the root or anchor of this system. Chronic eosinophilic activity leads to sustained acute neutrophilic inflammation. This in turn increases the exposure of endo-cellular auto-antigens, as well as "stirring" the architecture of the wound. Sooner or later, there is enough admixture, in time and in space, of endogenous antigen, antigen processing and presenting cells, and antigen receiving and immunizing cells. Once the latter phase of this process is reached, with antibody-bearing plasma cells, the wound cannot heal. It is auto-immunized. Knocking down the chronic-immune inflammatory cohort by specific pharmaceuticals allowed the wounds to heal.



45
Evidence of immunopathies affect wound healing

This case "proves" the point about auto-immunity impairing wound healing, by getting the wound to heal by knocking out the lymphocyte aggregates present in the non-healing wound. The patient is a 44 year old woman with chronic calcifying panniculitis of the right hip with progressive ulceration. This is a syndromic and usually progressive panniculopathy generally affecting pelvis & thighs, and seen with the connective tissue disorders (especially common with polymyositis). The photos show the lesion before definitive therapy, then healed 6 months later. The wound exhibited pathergy, with progressive necrosis with each attempt at debridement. There was no response to any topical care, and no response to intralesional or oral steroids. The graphs document progressive increases in wound volume (green) & area (blue) in spite of care. Histology confirmed lympho-plasmacyte infiltrates throughout the vascular locus. CD20 staining confirmed these as committed antibody producing plasmacytes. Cyclophosphamide was started as the most direct way to control lymphocytes (dose = 1 mg/kg/day). Wound improvements were immediate. Biopsy at 6 weeks showed restoration of normal wound and vessel features without the plasmacytes. The wound was healed within 4 months. After another 4 months of the wound & primary panniculitis remaining stable, the drug was tapered and withdrawn.

Top left, the wound while actively ulcerating, its base filled with calcific deposits and necrosis of the exposed tissues. Active ulceration is evident at the margins. **Bottom center**, the graph of wound volume and area shows progressive enlargement for the first few months. During this period, the patient opted out of any significant treatment due to personal affairs. When she finally gave consent for more deliberate therapy, the cyclophosphamide was started. Another reason for the enlargement was not just spontaneous progression of disease, but pathergy induced necrosis with attempted debridements and wound maintenance. **Bottom left**, wound biopsy shows dense lymphoid aggregates around vessels in the wound. The brown CD20 stains confirm that these aggregates are antibody producing B-cells. B-cells do not appear spontaneously. They are bred in response to explicit antigen challenge and recognition. **Bottom right**, biopsy of the wound a month into therapy, when the wound was now actively healing. The lymphoid aggregates are gone. That was the intended effect of the cyclophosphamide, and it succeeded in clearing those cells. Concurrently, and presumably a matter of cause-and-effect, the wound then started healing. The healed wound is seen **top right**, and it has now remained healed and stable over a prolonged interval. While it might be difficult to prove directly that lymphocytes inhibited the wound, it has been demonstrated that their clearance allowed healing to occur. The implication that auto-immunity, bred into the wound by its chronicity, has inhibited healing and further enlarged the wound cannot be ignored.

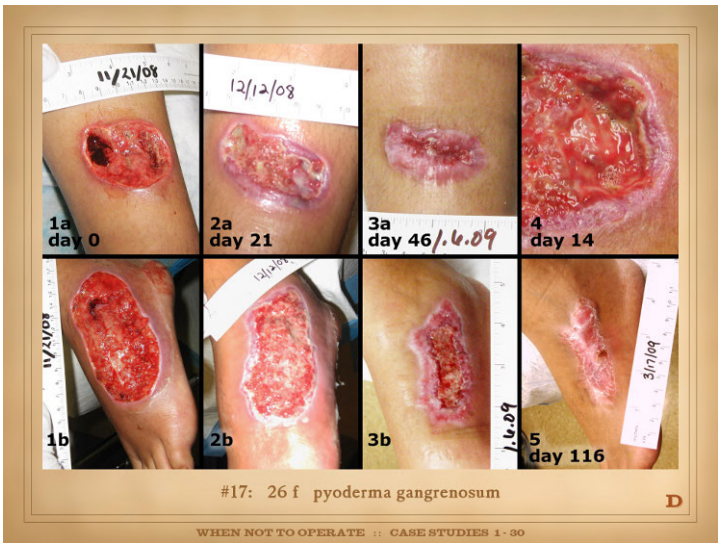


46
Case #16
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate common pyoderma gangrenosum.

This 50 year old healthy woman developed a lesion over the hip. It appeared spontaneously with no apparent instigation. It appeared as purpura with suppuration, eventually turning to dry eschar after treatment. The photos show that it was confined strictly to the dermis, sparing the adipose fascias underneath. This is paradigm pyoderma gangrenosum. The process was arrested with intra-lesional steroids, and it healed rapidly with basic topical care.

Pyoderma gangrenosum can occur in association with other, sometimes serious diseases. The other half occurs for no discernible reason in otherwise healthy people, which is this case. Many pyoderma cases are small and innocuous like this one, but the disease can be fulminant and systemically toxic when it involves large areas (see case #22). This process is notoriously prone to wound pathergy, and in fact pathergy is one of the hallmark features of the process. There is a joke (or a dictum?) among dermatologists to never let a surgeon see a case of pyoderma gangrenosum – they will only make it worse. The naive surgeon who debrides this without understanding the diagnosis and without pretreating with steroids is virtually guaranteed to cause progression of the problem, with new infarcts occurring along any incised margin.

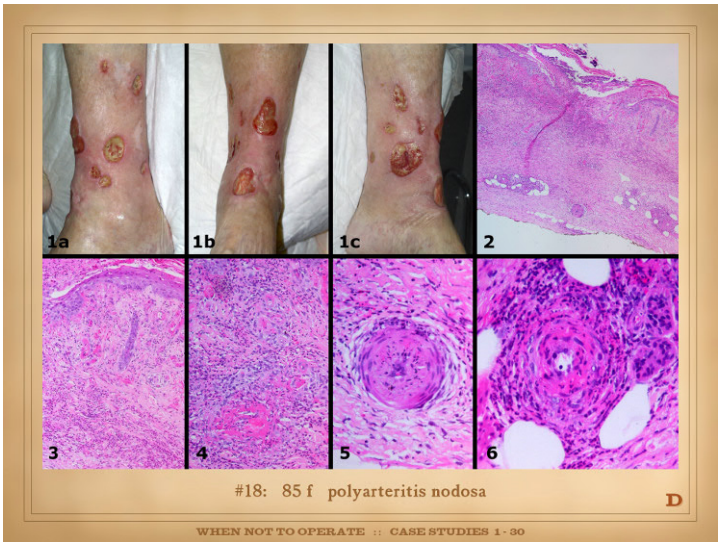
Figure 1 (day 0) shows distinctive features of the pyoderma lesion, about 3 weeks after onset of the process. The eschar is skin only, and it is separating. The hypodermis is healthy and starting to heal. There is no peri-wound inflammation, and the disease itself has been quiet for 2 weeks. **Figure 2** (day 49) shows the wound completely reepithelialized. These images show that as long as the causative disease is arrested, the wound will behave as a normal wound, and eschar will eventually separate. There is no need for exogenous debridement which is a risky intervention for active pyoderma.



47
Case #17
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate disease-associated pyoderma gangrenosum and the risk of wound pathergy.

This 26 year old woman had Hodgkin's lymphoma. Periodic disease recurrence prompted periodic retreatment, but she had stayed healthy and mostly disease free for several years. The current leg and foot ulcers occurred during one of her episodic recurrences and treatment cycles. Presenting as several purpuric lesions of the skin, an initial biopsy or debridement resulted in progression of the problem. When seen in consultation, the lesions were easily recognized as classic pyoderma gangrenosum. This case is nearly identical to the preceding (case #16), except that this one is associated with another disease (and one that explicitly involves the lymphoreticular system). Intralesional steroids were injected, and oral steroids were started. The disease was thereby arrested, then the eschar was debrided, and then the lesions all healed with basic topical care over 2 - 3 months (and the patient remains free of active Hodgkin's). There is a tendency for surgeons to want to excise or debride these lesions, but trauma must be avoided to prevent pathergic progression of the infarcts. The sooner that steroids are given, the sooner the problem extinguishes. While half of pyoderma is incidental in healthy people, its occurrence should prompt a history and system review to screen for immune and hematological diseases.

Figure 1 (day 0) shows the left anterior leg **(1a)** and dorsal foot **(1b)** about 2 weeks after the onset of the problem, and 1 week after intralesional steroids were given and oral steroids started. No images are available of the original skin infarcts, but a few remaining scraps of eschar are still visible. Note the preservation of the subcutaneous adipose, typical of pyoderma. **Figure 2** (day 21) and **figure 3** (day 46) show progressive healing with basic hygienic wound care, without any flareup of the primary pathology. **Figure 4** is a closeup of the leg lesion at day 14. There is a fully expressed wound module with significant epithelial ingrowth, confirming that wound healing kinetics are unhampered by pyoderma (once the disease is fully controlled). **Figure 5** shows the foot lesion at 4 months, healed and stable.

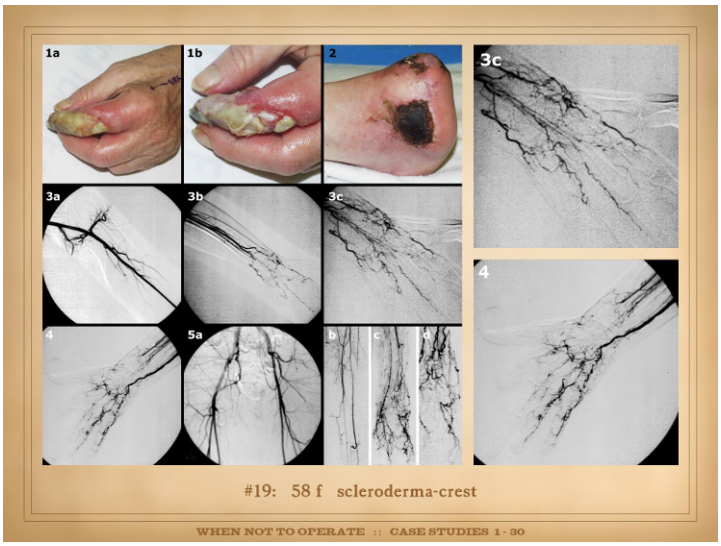


48
Case #18
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate wound and soft tissue complications of auto-immunopathies and vasculitis.

This 85 year old woman presented with multifocal leg and ankle ulcers. They were prototypical immunopathic ulcers, with gross features of vasculitis, synovitis, and panniculitis. The patient gave no history of prior major illness, but review of systems was positive for a variety of immunopathic symptoms, and laboratory evaluation was positive for low level rheumatoid and lupus serologies. Histology showed a neutrophilic vasculitis and perivasculitis along with acute and chronic microthrombi, vascular necrosis, and microvascular fibrosis and stenosis, findings typical of leukocytoclastic vasculitis or especially polyarteritis nodosa (PAN). The wounds healed unexpectedly well with just steroids and topical care, but over the course of one year, there were several recurrences. The last flare up caused sufficiently large ulcers and tendon exposure that surgical coverage was planned, using a collagen-gag regenerative matrix so as to avoid the certain pathergy and wound problems that would complicate conventional cut-and-sew surgery. However, the patient became progressively ill and died before surgery could be done. The sudden appearance, severity, and recurrence of these lesions was typical of autoimmunopathy out of control. Most physicians might think of end stage lupus or rheumatoid (or Behçet's or Wegener's or PAN, etc.) as being characterized by intense arthritis, nephritis, pericarditis, pneumonitis, cerebritis, gastro-intestinal ulceration, opportunistic infections, or similar dramatic visceral events, but there is a certain group for whom the terms "collagen vascular disease" and "connective tissue disorder" live up to their namesake. In these patients, occult or non-obvious markers of disease can be found on evaluation, but the presenting features and the most overt signs and symptoms are dermal or subdermal vasculitis, panniculitis, and synovitis with resulting skin ulcers. The presenting profile of this patient is highly correlated with end stage autoimmunopathy and mortality.

Figure 1 shows lateral, anterior, and medial views of the left ankle. The anterior ulcers **(b)** are along the tibialis tendon, consistent with a synovitis, whereas the others extend into the subcutaneous tissues due to vasculitis or subdermal panniculitis. The remaining figures show various histological features of these immunopathic wounds (from a biopsy of one of the lesions). Seen in overview in **figure 2**, there is skin ulceration over an area of concentrated acute inflammation, but it is the surrounding tissues which are more revealing. There is chronic wound healing and wound module at the margins of the ulcer, including epithelial migration. At the base of this activity is a lamina of acute inflammation, in what would be the subpapillary network in normal skin (between papillary and reticular dermis), or the inflammation-free fibroplastic layer in a normal wound. It is easy to see that the ulcer occurs in an area where this tangential inflammation has become more intense. Since the papillary

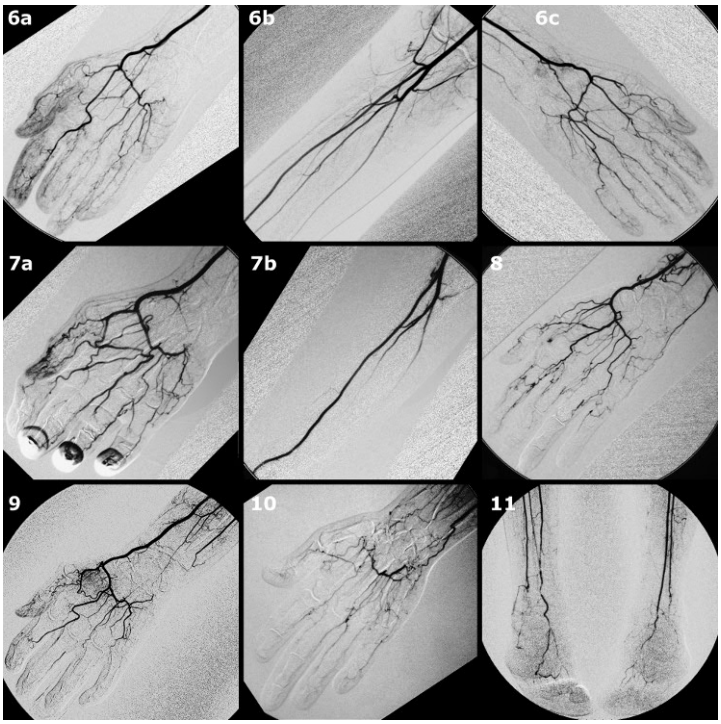
dermis is merely the vessel-dense lamina propria for the epidermis, it is not surprising that vasculitis is active through this layer. Deep to this, in the reticular dermis, larger vessels have inflammatory infiltrates, without surrounding abscess or generalized fibrositis, characteristic of polyarteritis nodosa. **Figure 3** is a closeup of the wound module at the ulcer margin, with the inflammatory lamina below, a finding which would never be seen in a benign healthy post-traumatic wound. **Figure 4**, from the subpapillary or interlaminar zone shows intense perivascular inflammation with fibrinoid degeneration of vessels. **Figure 5** shows a larger dermal vessel with chronic thrombosis, inflammation, and fibrosis. **Figure 6** shows the acute primary vasculitis, with infiltration of the vessel wall, fibrinoid changes, and intense peri-arterial leukocytic inflammation. The cells are nearly all neutrophils, including a lot of "poly dust" (nuclear debris). As with the other micrographs shown in this review, chronic ulcers and pathological wounds, and the surgical risks that they carry, are due to demonstrable anatomical disease.



49
Case #19
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate wound and soft tissue complications of auto-immunopathies and vasculitis.

This 58 year old woman with scleroderma-crest developed an inflammatory ulcer of the finger and dry escharotic infarcts of the foot (She also had a more generalized lupus component of her disease, and she was already missing other fingers and toes). The referring physician's notes document "she received a paper cut [one month ago] to the middle phalanx of her left index finger and this has gone on to become a fairly large eschar involving the dorsal aspect of the proximal and middle phalanx." Those notes also described "ongoing skin slough involving the transtarsal amputation" (the amputation, performed four years earlier, was healed until these new acute events). Workup was done for relevant immune, vasculopathic, and hypercoagulable states. Arteriograms confirmed the presence of advanced "lupus-scleroderma angiopathy" and severe digital ischemia. For this patient, angiolysis and digital sympathectomy were done in foot and hand, with DIP amputation of the finger and skin grafts to the foot, supported with steroids and hyperbaric oxygen therapy, resulting in complete healing. The loss of a finger due to a simple paper cut is a paradigm example of wound pathergy: minor trauma, major catastrophic complication. Pathergic complications are apt to occur in patients with vascular or other occlusive-ischemic disorders or else immune-inflammatory disorders. A patient with scleroderma-crest has both risks. Imagine that that paper cut had been an unwary operative incision, and it is now easy to understand why surgery done without disease management or pre-operative preparation against pathergy will assure enlargement of the problem (see cases #26, #27, #29).

Figure 1a is the ulcerated index finger just prior to amputation. **Figure 1b** is a closer view, after removing some eschar, confirming destruction of the extensor mechanism and joint capsule. This is the result of a "paper cut" in an ischemic finger. **Figure 2** shows the foot with multiple areas of escharotic skin. The angiograms confirm the typical arteriopathy of scleroderma-crest (see addendum images below for more information). In **figure 3a**, the brachial artery and branches in the arm are normal. In the forearm, **figure 3b**, there is a transition from normal vessels proximal to pathological vessels at the wrist and into the hand (hand closeup in **figure 3c**). **Figure 4** shows comparable disease in the other hand. **Figure 5** shows the lower extremity. The ilio-femoral vessels are normal (**figure 5a**), but at mid leg, the tibial and peroneal vessels develop the same type of segmental stenoses and occlusions that are present in the hands (**figure 5b**). **Figure 5c** shows disease across the ankle, comparable to the disease at wrist and hand. **Figure 5d** is a closeup at the ankle showing more detail about the morphology of the affected vessels. Severe ischemia is obviously a consequence, putting hand and foot at risk for pathergy and necrosis in the event of any trauma or inflammation.



49b
Lupus-scleroderma angiopathy

Addendum images. Observe in the patient's angiograms above that disease occurs only acrally, that vessels are normal proximal to elbow and knee. Observe that while the left wrist had advanced disease involving both major vessels, that disease is radial dominant on the right, the ulnar artery spared enough to allow some flow into the hand. Note the numerous segmental stenoses and occlusions, the corkscrew or "unwound" appearance of non-stenotic vessels, and the patchy obliteration of the palmar arches and digital vessels. These are the characteristic, actually pathognomonic changes of lupus or scleroderma-crest angiopathy.

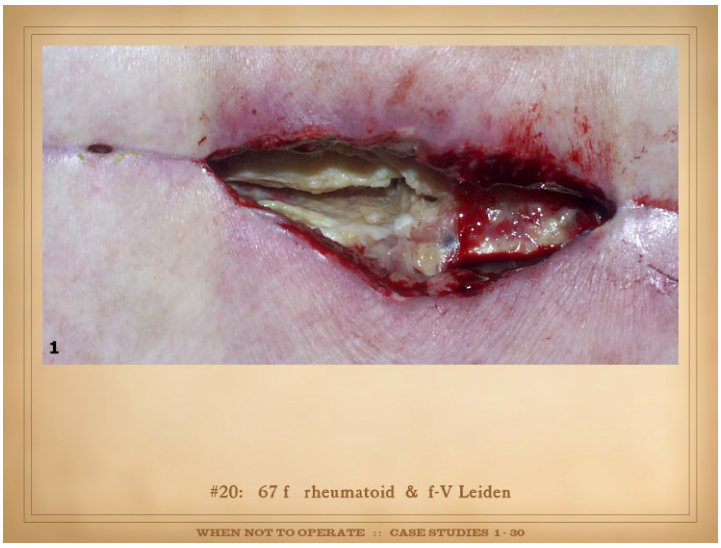
Lupus-scleroderma angiopathy is the non-atheromatous fibro-stenotic arteriopathy that results from long standing auto-immune activity with some of the connective tissue disorders. It is typically most readily appreciated with scleroderma-crest, indeed a common or hallmark feature of that disease, but it also occurs with lupus. Hypothetically, it might occur with any of the cvd-ctd's, and it ought to be considered in any such patient having digital ischemia and ulceration, but as a practical matter, it is seen with scleroderma-crest and with lupus. It might seem "obvious" to attribute this to an active inflammatory autoimmune vasculitis, inasmuch as "-itis" and vasculitis are common features of these diseases, but the histopathology is one of fibromuscular hypertrophy and hyper-lamination of the vascular media without acute or neutrophilic inflammation ever being present. It is thus comparable to the generalized or systemic sclerosis of scleroderma which is not overtly inflammatory and which is often not treated with anti-inflammatory corticosteroids

• This process is more prevalent in the upper rather than lower extremities. • It centers on the wrist or ankle, advancing proximal and distal into forearm-leg and hand-foot as the disease progresses. • It always remains strictly and exclusively acral, distal to elbow or knee, never occurring proximal to those levels. Indeed, the more central vessels are often perfectly healthy, even juvenile looking, never with any hint of atherosclerosis or similar degenerative angiopathy. • It also tends to strongly affect one side or the other, ulnar or radial, more often ulnar, but both sides can become involved as disease progresses.

Raynaud's vasospastic episodes, representing vascular reactivity when vessels are still capable of such, are a prelude to more advanced histological disease. Vasospastic episodes can still occur even when advanced long-segment stenosis is present. It is important to understand though that ulcers and infarcts do not occur until there is anatomical disease with sustained ischemia, and that once ulceration occurs, the problem is no longer simply "Raynaud's". Improved circulation with ulcer healing and relief of ischemic pain is reliably achieved by sympathetic blockade and angiolysis. Short term therapy and symptomatic relief can be done by local anesthetic blockade of the vessels in the wrist and hand (and or stellate ganglion blockade). More definitive therapy with sustained effects leading to healed wounds is done by "digital sympathectomy". This is a surgical adventitial stripping and fibro-myectomy of vessels in wrist (or ankle) and within the hand which eliminates the sympathetic nerves and the stenotic vascular segments. Botulinum toxin blockade of wrist and hand vessels, in lieu of operative angiolysis, can have the same effects and good results as operative angiolysis (the effects of botulinum blockade typically last 4 to 9 months).

Because this pathology occurs with connective tissue disorders, the possibility of concomitant hypercoagulability must always be considered and evaluated. A hypercoagulable state in the presence of flow stasis and thrombogenic surfaces is a bad combination, and all components of the problem must be treated. In the following examples, none of these patients had diabetes nor any other form of calcific atherosclerosis, just lupus angiopathy. **Figure 6** shows disease from a patient with lupus and finger ulcers (48 year old woman). Vessels in the proximal forearm and above the elbow are normal (**figure 6b**). The characteristic changes described above are present throughout the wrists and hands (**figure 6a** is right, figure **6c** is left). Note that disease is ulnar dominant on both sides. **Figure 7** shows the same changes in another patient with lupus (49 year old man). The hand has the same characteristic features with ulnar dominant disease and diffuse patchy obliteration of digital vessels (**figure 7a**). Disease starts at mid-forearm, with the antecubital vessels (and everything proximal) being normal (**figure 7b**). **Figure 8** is from a 62 year old woman with scleroderma-crest, with the same changes and ulnar dominant disease. **Figure 9** is similar, from a 62 year old woman with scleroderma-crest. **Figure 10** is also similar, from a 50 year old woman with scleroderma-crest, but with radial dominant disease. (Native ulnar artery is also occluded across the wrist but is bypassed by natural collaterals.) **Figure 11**, from a 66 year old woman with scleroderma and lupus, protein S deficiency, and foot ulcers, shows similar disease starting just above the ankles (with otherwise clean vessels at all higher levels).

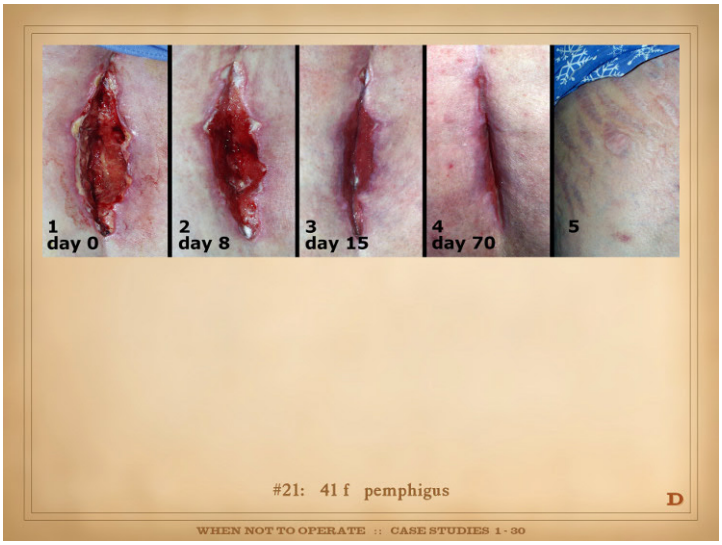
Every one of these patients presented with severe ischemic changes and symptoms, with ulcers of fingers or ankle or toes. Every one had normal arteries proximal to elbow and knee. Everyone had active autoimmune disease. Everyone was healed after angiolysis along with miscellaneous other relevant care. Prior to definitive care, all had had prolonged ineffective treatment with vasodilators or other naive therapies for "Raynaud's", treatments that cannot correct this advanced state of anatomical angiopathy. For the main patient of case #19, the acute presentation was due to wound pathergy following trivial trauma. For some of these other patients, they too had some minor finger injury, whereas for others the problem began with spontaneous scleroderma ulceration. All were at risk for wound pathergy and complications if indiscriminate surgery would have been done without acknowledging the disease and peremptorily treating the risks before surgery. Yet all had successful uncomplicated surgery (digital sympathectomy) with healed wounds by a priori planning for these risks.



50
Case #20
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate wound pathergy and surgical complications associated with a collagen-vascular disease.

This 67 year old woman had a 20 year history of active rheumatoid and crest, maintained with steroids. She had decompressive laminectomy and fusion for arthritis related problems. The back wound failed. The photos show necrosis at the skin margins and throughout the wound. She had a family history of venous thrombosis, and work up confirmed factor V Leiden heterozygote, plus high fibrinogen with reflex markers of a hypercoagulable state (protein C and plasminogen elevated). She was started on warfarin, the wounds were cleaned up by a period of topical care, and then surgery was done to close the wound (paraspinal muscle flaps and direct skin advancement).

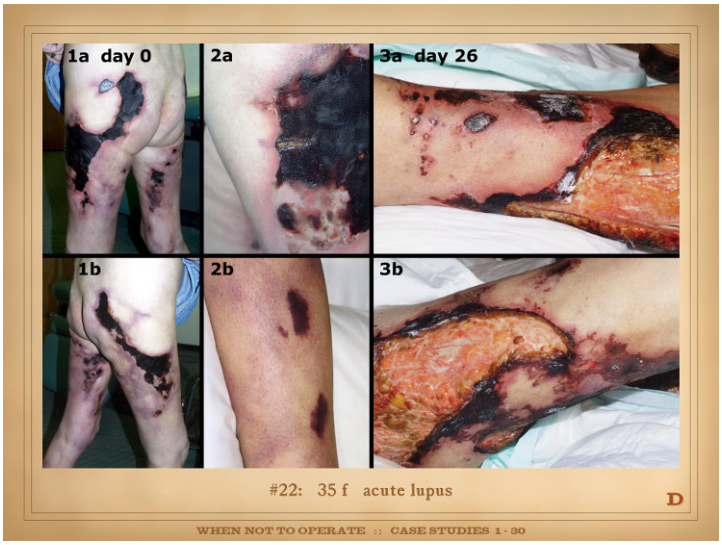
Figure 1 shows the lumbar back wound 5 weeks after surgery. Wound module proliferation has started in some of the tissues, but residual necrosis and eschar are present at wound margins and in musculoskeletal structures at the base. Had this surgery been done in an otherwise healthy patient for trauma or degenerative joint disease, this complication would have been unlikely to occur. It is of course possible that that trauma or djd patient could coincidentally have a pathergy prone underlying risk, such as an occult hematological or hypercoagulable disorder. Patients and surgeons alike can never be fully protected from that which is categorically unseen and unknown until it does its unanticipated damage. However, if pathergy prone diagnoses are appreciated in advance, then problems like this can be oftentimes be avoided. This patient had no antecedent diagnosis of a hypercoagulable state (the diagnosis was made due to this event), but the rheumatoid history was clear, and that was enough of an alert to ask about all such potential problems in the patient interview and review of systems.



51
Case #21
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate wound pathergy and surgical complications associated with an immune dermatosis.

This 41 year old woman was treated for several years for pemphigus vulgaris. She took prednisone 180 mg daily (she stated that other anti-immune therapies had not been effective). The high prolonged steroid doses resulted in lipomatous hypertrophy of various tissues. One such lipoma caused acute spinal cord compression and paraparesis requiring emergency laminectomy and decompression. The back incision failed. The photos show multifocal infarcts and lysis at wound margins. Her pemphigus lesions had been under control, so it is uncertain if this was ulcerative wound pathergy due to autoimmune flareup versus simple dehiscence due to steroid-induced wound healing insufficiency. Coagulopathic workup was negative. (Much is talked about wound healing negative effects of steroids. Steroids are generally benign for wounds, and their ability to control disease is actually the cornerstone of good wound healing when underlying immune and inflammatory disorders flare and cause ulcers. To the extent that they have a negative wound effect, it is not a generalized pan-physiological inhibition of the process. Most of the process works properly, at least qualitatively, even if some proliferative features are slowed or quantitatively diminished. Their most obvious negative effect is on collagen deposition. Wounds heal but they are not strong nor stand up to ordinary physical forces. Dehiscence, if it occurs, is from mechanical rupture rather than infarctive or inflammatory ulceration. The entity is real but seen under only a limited set of extreme circumstances, such as high load wounds, e.g. laparotomy in a patient with chronic steroid-dependent bronchitis, or with very high cumulative steroid doses, as in this case.) The wounds nearly healed with vitamin A and topical care, and her paresis gradually started to recover. Being off of her usual anti-inflammatory doses, there was a flareup of her autoimmune state, with multiple system failure, from which she died before the wound was finally and completely closed.

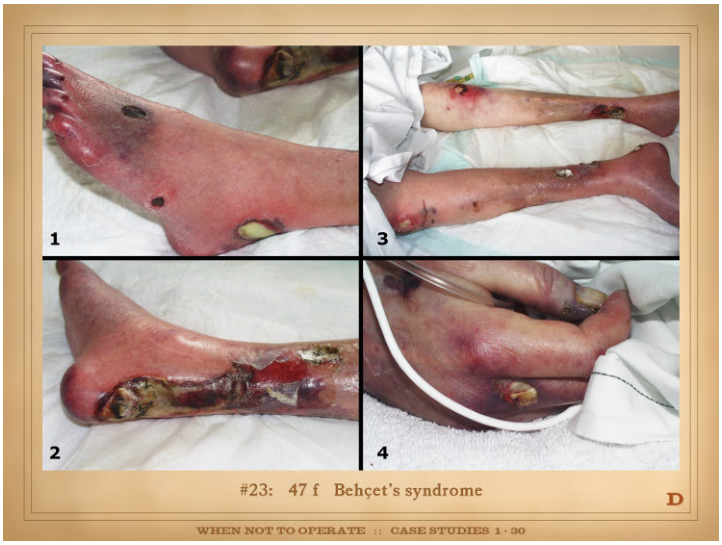
Figure 1 (day 0) is the wound on initial consultation, 4-5 weeks after lower thoracic laminectomy. Acute events are subsided. Some residual infarcts and eschar are visible at skin margins and base of the wound. The wound surface has a red blush suggestive of wound angiogenesis (aka "granulation tissue"), but close examination shows that fat lobules and muscle and fascia bundles are still all visible, so wound proliferation and repair dynamics are significantly retarded. **Figure 2** (day 8) shows less eschar, with the onset of more normal proliferative angiogenesis and of wound contraction. These favorable behaviors have accelerated toward normal after initiating pharmacological doses of vitamin A to counteract the wound-negative effects of steroids (which had by now been lowered to low therapeutic doses). At day 15, **figure 3**, the wound is behaving normally, and by day 70, **figure 4**, it is nearly healed. **Figure 5** shows obesity and striae of the trunk due to the extraordinary corticosteroid doses she had been on (and she had various other Cushingoid features as well). This case is a reminder that both severe immunopathies and their various treatments can have active pathergic effects on wounds and also detrimental effects on wound healing. Common wound-healing adverse drugs include certain antimetabolites (e.g. hydroxyurea), TNF-a inhibitors, rapamycin, and some others.



52
Case #22
(Set 6, immune & inflammatory disorders, and wound pathergy)
A case to illustrate skin and soft tissue infarcts due to acute immunopathic states.

This 35 year old woman developed acute lupus shortly after pregnancy and delivery. An extremely morbid event with severe liver and renal failure, she lived through it due to general critical care and aggressive treatment of the primary disease. She developed large skin infarcts as part of the acute process, which had turned to dry black eschar by the time of consultation. The differential diagnosis includes a variety of immune and hematological ulcerogenic or necrotizing states, all related one way or another to lupus. Pyoderma gangrenosum is one likely state, and multifocal toxic pyoderma of the central body is an event that has happened to other post-partum patients. However, in this patient the necrosis involved subcutaneous fascias as well as skin, a distinctive difference from usual pyoderma. Fascial necrosis implies immune panniculitis or a non-immune micro-thrombotic disorder. Immune panniculopathies would include the classic connective tissue disorders (lupus, Behçet's, Sjögren's, etc.) plus the various primary panniculopathies such as eosinophilic fasciitis and necrobiosis lipoidica (Weber-Christian is perhaps the most prevalent of these panniculopathies, but it has an erythema nodosum type of presentation and histology and it is not likely to cause escharotic infarction of this variety). Absent biopsies during the acute phase, these pathologies could not be discriminated histologically. Workup for micro-thrombotic disorders showed that this patient had protein S deficiency accompanied by low transcutaneous oxygen pressures in the affected areas. The general appearance of the skin and wounds is more thrombo-occlusive than inflammatory-lytic, so a hypercoagulable state most likely contributed much to the mix that caused these infarcts. Her primary immune-inflammatory state was still active though, and conventional skin grafts or other surgical repair, which carry a very high risk of wound pathergy, were not even attempted. Instead, she was treated by a pathergy-controlling strategy of excision and closure with a collagen-gag matrix and hyperbaric oxygen support. The reconstruction was not completed because, following a dose of cyclophosphamide, she became severely neutropenic leading to mycotic brain abscess and death.

Figures 1a, **1b** show the skin infarcts of the pelvis and lower extremities. **Figure 2a** is a closeup showing the boundary between eschar and living skin. **Figure 2b** is another closeup showing foci of intense vascular stasis which are not yet escharotic, but which will probably die. The absence of edema and other significant inflammatory changes, and the generalized skin purpura and cyanosis are characteristic of thrombo-infarctive pathologies rather than immune-inflammatory. In spite of the overt diagnosis of a collagen-vascular disease, workup must also look for hypercoagulable states which are likely to accompany the immune disorder. Shortly after these images, the large eschars were excised and the wounds covered with Integra™ collagen-gag matrix. **Figures 3a** (left thigh) and **3b** (right thigh) show the skin one month later, after disease flared up again, causing new infarcts. While the collagen-gag matrix is protective against acute wound pathergy when underlying disease has some degree of control, it cannot protect against flagrant active disease. Note especially the eschar along the borders of the excisions, characteristic behavior of pathergy prone disorders.



53
Case #23
(Set 6, immune & inflammatory disorders, and wound pathergy)
Another case to illustrate skin and soft tissue infarcts due to acute immunopathic states.

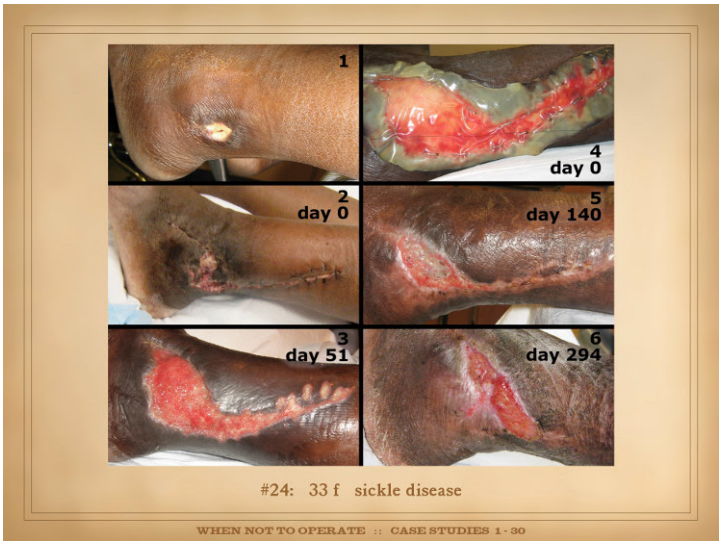
This 47 year old woman was treated for several years for progressive neurological problems attributed to multiple sclerosis. At the time of these photographs, she had developed multiple acute morbidities, including a dense neurolepsy, respiratory failure, and multifocal skin infarcts on multiple areas of the body. History and physical confirmed a multitude of immunopathy related symptoms and signs, qualifying this as a lupus-like or mixed connective tissue disorder. Strong features included a history of uveitis and oral and genital ulcers, which in conjunction with the nature of the skin lesions made Behçet's syndrome the "best fit" diagnosis. Cerebral angiograms confirmed a diffuse angiopathy consistent with acute and chronic vasculitis. Given the dismal mortality statistics for untreated acute lupus and Behçet's, it is no surprise that the patient died. As seen in the photographs, not only were skin infarcts severe, but preliminary debridements simply resulted in more of the same, a prototypical example of Behçet's skin pathergy.

Figures 1, **2** are views of the feet and ankles showing multifocal infarcts in patterns consistent with small vessel and microvascular thrombosis, pressure injury (thresholds lowered by vascular insufficiency), and synovitis. Along with all of the new infarcts, areas of prior ulceration or debridement at the malleolus and calcaneus have a ring of black necrosis at the skin margins, the kind of pathergy which can affect surgical

incisions in predisposed diseases such as Behçet's syndrome and pyoderma gangrenosum. **Figure 3** is another view of the lower extremities illustrating the extent of the problem. The same spectrum of problems also occurred elsewhere, including trunk, face, and upper extremities, as seen on the hand in **figure 4**.

54
Set 7: Proscription against surgery

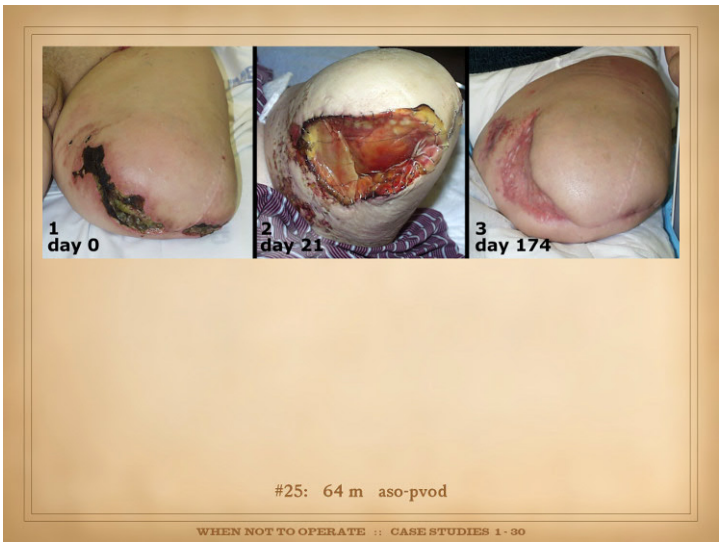
There are times and situations when surgery must not be done. Conditions of ischemia and altered immunity or inflammation that put wound or patient as a whole at risk for profound and progressive morbidity or fatal complications must be corrected before surgery is done. This set of cases illustrates the kinds of wound pathergy, wound failure, and clinical complications that arise from at-risk disorders, validating why surgery ought not to have been done or else delayed until properly prepared for.



55
Case #24
(Set 7, proscription against surgery)
Wound pathergy due to a red blood cell disorder, the wound made worse by surgery.

This 33 year old woman with sickle disease had a chronic ulcer of the lateral ankle, unresponsive to a variety of therapies. An attempt was made to close the wound by some sort of local skin advancement. It did not heal – the wound failed – and what had been a small ulcer was now a large ulcer with the same problems along all of the incisions. Upon consultation, it was opted to reconstruct skin using one of the most dependable strategies there is for controlling wound pathergy and healing at-risk pathological wounds: preparatory wound care, then closure with a collagen-gag regenerative matrix (Integra™), supported by hyperbaric oxygen therapy (because of the micro-occlusive nature of the problem and confirmed low transcutaneous oxygen tensions). This approach eliminated further complications, and the wound almost fully healed. However, the patient's life, including plans to touch up and conclude the reconstruction, was interrupted by numerous sickle crises and hospitalizations. The ulcer persisted, but with time, the patient accepted it as a chronic condition, and was able to keep it stable with good hygienic topical care. Had the original conventional cut-and-sew surgery not been done, the problem, even if it did not heal, would have remained small and easier to manage.

Figure 1 shows the original ulcer on the lateral left ankle. **Figure 2** (day 0) shows the ankle after attempted closure. Listed in the medical record as a "rotation flap", this improper design would not have covered the wound under the best of circumstances, and in this patient with a pathergy prone micro-occlusive disorder, flap necrosis and wound failure were predictable. **Figure 3** shows the ankle 51 days later after a return to basic topical care. The wound is clean, free of further injury, and proliferating. Nonetheless, as a pathological wound, wound module kinetics are impaired, and the wound failed to make any further improvements after 3 months of topical care. **Figure 4** (designated as a new day 0) shows the wound with Integra™ collagen-gag matrix in place, the start of a regenerative skin reconstruction using a pathergy-preventing matrix. **Figures 5, 6** show the reconstruction 140 and 294 days later. The remaining wound appears healthy, and in a healthy person it would easily epithelialize to complete closure. However, the patient's progress was interrupted by numerous sickle crises, and it got no better. For the sake of further management, the judicious and economically circumspect use of new layers of regenerative matrix or of topical stimulatory therapies are all worthy and justifiable, since they incur no further risk to the patient. Conventional therapies such as transfusion (erythrocyte exchange) and rheological drugs are always worth trying. Doing more of conventional surgery with incisions and repairs would be improper and subject to the same complications.



56
Case #25
(Set 7, proscription against surgery)
Wound pathergy due to macro-arterial disease, with preventable complications due to indiscriminate surgery.

This case illustrates the one type of wound pathergy that most surgeons have at least some awareness of, progressive amputations due to arteriosclerotic peripheral occlusive disease. This 64 year old man with hypertension and atherosclerosis developed a small ulcer or infarct on the foot. Foot or toe amputation was followed by below-knee amputation and then above-knee amputation which likewise infarcted. The progressive amputations were obviously done because of necrosis and wound failure at each prior level. The patient was seen in consultation after having been threatened with hip disarticulation, which would also have died, inasmuch as the patient had Leriche syndrome and high grade aorto-iliac stenosis. The thigh-level infarct was resolved and healed by usual modalities (preparatory wound care, closure with Integra™ collagen-gag regenerative matrix, and hyperbaric oxygen support). Wound pathergy was due to severe ischemia. While a macro-vascular disease was the culprit here, the same risks accrue to any vaso-occlusive disorder. The principles, arts, and techniques of peripheral vascular surgery have now been with us for a long time, e.g. the first abdominal aortic replacement and femoral-popliteal bypass (1956), clear enunciation of the principles of limb salvage (c1970), and the advent of vascular endo-technologies (c 1995). These have all made revascularization a reasonably dependable low morbidity affair available in most communities. Nonetheless, too many patients have indiscriminate surgery on ischemic limbs by unwary or uneducated surgeons resulting in completely preventable major morbidity and disability. For this patient, operative revascularization became impossible once the thigh amputation was done, but proper management from the beginning would have corrected the problem and preempted all subsequent issues. At any point along the way, prudent wound care and wound reconstruction would have solved the problem at a lower level. The indiscriminate use of surgery in patients with pathergy-producing risks is disallowed. Proper diagnosis and peremptory management before further surgery are mandatory.

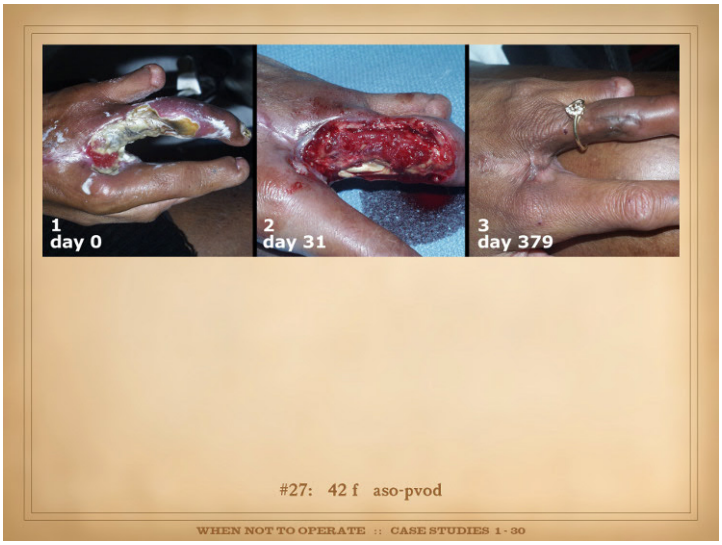
Figure 1 (day 0) shows the thigh following recent amputation, just prior to threatened hip disarticulation. Disarticulation could not have been condoned for any number of reasons, but even assuming that it had some theoretical legitimacy, it would have had the same pathergic necrosis of the incision, since the level of vascular occlusion was well above the blood supply to the hip. **Figure 2** (day 21) shows the thigh after excision and closure with pathergy-controlling Integra™ collagen-gag regenerative matrix. **Figure 3** (day 174) shows the thigh fully healed. By understanding the relevant pathologies, unexpected post-operative necrosis and complications can be anticipated. By using appropriate strategies and methods, wound necrosis can then be preempted. Had these principles been exercised when the problem was confined to the foot, significant amputation likely would not have been needed. Sadly, because he had central large vessel (rather than peripheral small vessel) atherosclerosis, he easily could have been cured by aorto-bifemoral bypass or endoprosthesis, allowing the original foot problem to heal. This corruption of proper care reflects that despite the robust knowledge and art of such things, physicians are graduating from school and residencies without such foundational and conceptually basic knowledge. The medical system and errant doctors are as much to blame as the native diseases, or more so, for the problems seen in this set of cases, thus the "proscription against surgery".

57
Case #26
(Set 7, proscription against surgery)
Another wound pathergy due to arterial disease, with preventable complications due to indiscriminate surgery.

Diabetes mellitus and its complications are epidemic among native peoples of the American southwest. Unlike other groups where atherosclerosis is associated with hypertension, smoking, hyperlipidemias, and other risk factors (including diabetes), the vascular disease in this population can result in severe distal occlusive disease of the upper extremity. This 51 year old man had a small injury or infarct of his fingertip. Attempts to debride it turned a small problem into a progressively bigger problem. As seen in the photos, at the time of consultation, the wound surfaces after recent debridement-amputation were all necrotic. Wound stability and the slow induction of a proliferative wound module were contingent on basic hygienic wound care, judicious piecemeal debridement of separating eschar, wound stimulatory therapies, and especially on doing no further surgery. Conventional surgery simply creates a new level of injury and pathergy affecting still viable tissues, unnecessarily extending the wound. Partial finger amputation may have been unavoidable, but had any of the strategies for preventing pathergy been used, the problem would never have progressed proximal to the metacarpophalangeal joint. (The patient died from other complications of diabetes, renal, and vascular disease before his hand healed.)

Figure 1 (day 0) shows the dorsum of the left hand. The ring finger debridements progressed to the ray amputation seen here, and the resulting

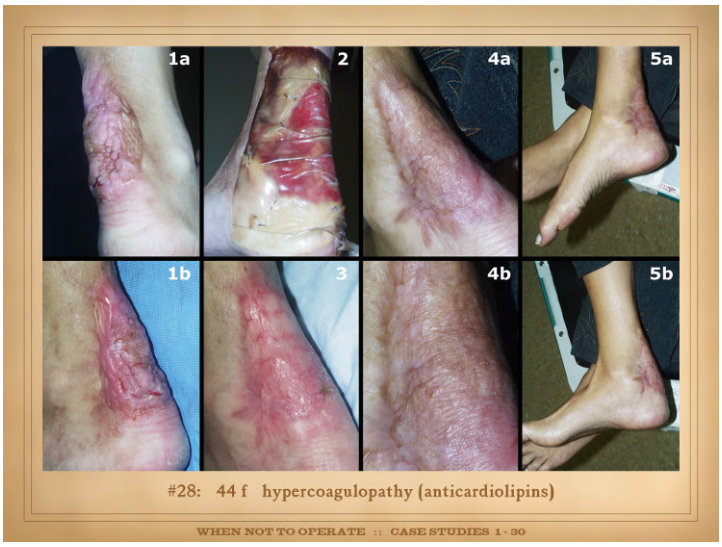
wound has necrosis of all exposed tissues. **Figure 2** (day 17) shows that although the wound is not yet healing, that necrosis has been arrested with proper care. **Figure 3** (day 90) shows that: there is no further necrosis; eschar is mostly gone (other than some tendons left in the hope they might be partially salvaged); a proliferative wound module has appeared; there is early epithelial growth at some of the margins. **Figure 4** (day 115) shows a healthy wound with progression of these positive changes, including wound contraction and significant epithelialization. Had the patient survived, the wound was at the point where closure could have been done by continued topical care in support of natural contraction, versus skin grafts, versus a regenerative biomatrix (e.g. Integra). The biomatrices are the best options for these situations, since they effectively close the wound without additional injury and thus preempt all pathergy producing physiology.



58
Case #27
(Set 7, proscription against surgery)
Another wound pathergy due to arterial disease, with preventable complications due to indiscriminate surgery.

This is similar to the preceding case, a 42 year old woman, southwest native American with diabetes and upper extremity athero-occlusive disease. A small ulcer of the long fingertip, followed by overly ambitious attempts to cure it with surgery, resulted in progressive necrosis and amputation, resulting eventually in ray amputation and necrosis of the adjacent finger. Progressive surgery simply meant progressive displacement of the zone of active infarction to an ever more proximal position. When seen in consultation, active necrosis and progressive ulceration were arrested by basic pathergy-controlling modalities (hygienic topical care with silver sulfadiazine, judicious debridement of separating eschar, and eventual closure with Integra™ collagen-gag regenerative matrix). Had these modalities been initiated at the beginning in lieu of surgery, the rest of the story would never have happened.

Figure 1 (day 0) shows the left hand after multiple failed attempts to cure ischemic ulceration with more surgery. At the time of presentation (not illustrated here), the dorsum of the hand in the third ray was completely necrotic. A period of basic wound care (hygiene, silver sulfadiazine) arrested the infarcts and allowed the wound to start healing, (as seen in this photo, with dorsum of the hand already healed by natural contraction). The partially necrotic ring finger requires some sort of pathergy-safe closure. **Figure 2** (day 31) shows the ring finger at the time of debridement and closure with Integra™ collagen-gag regenerative matrix. **Figure 3** shows the hand healed at one year. Had these principles of care and pathergy avoidance been applied from the outset, the patient would have lost only a fingertip.

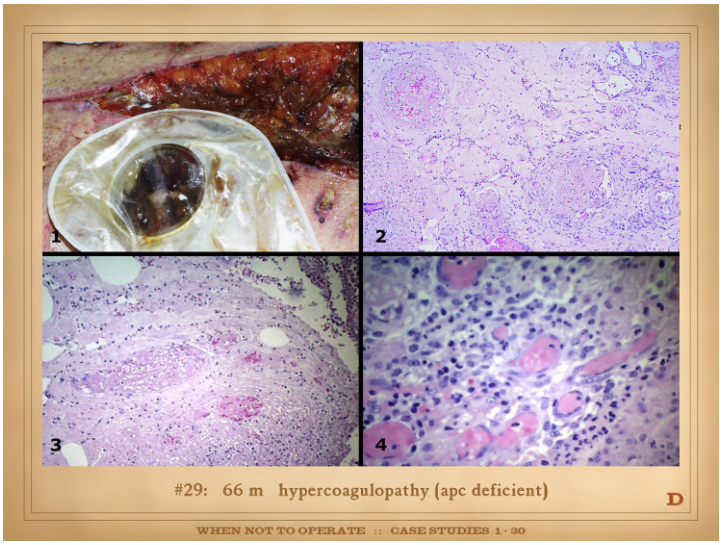


59
Case #28
(Set 7, proscription against surgery)
Another wound pathergy due to a micro-thrombotic disorder, with progressive ulceration due to repetitive surgery.

This 44 year old woman had an achilles tendon rupture during exercise. Attempted repair was complicated by necrosis of the overlying skin. Multiple repair attempts caused more necrosis. Eventually, the wound was covered with a rectus abdominis free flap which did heal, but the overlying skin grafts became chronically ulcerated and painful. Attempts to repair or revise them also resulted in skin necrosis and persistent ulceration. The patient's history was significant for blindness in one eye due to retinal artery thrombosis. This history is highly suggestive of a hypercoagulable disorder, and when seen in consultation, laboratory evaluation showed high anticardiolipins and fibrinogen, confirming an antiphospholipid antibody syndrome. Warfarin anticoagulation was started, and then the old dysplastic grafts and ulcers were excised, and skin was reconstructed with a pathergy-controlling collagen-gag regenerative matrix (Integra™). The ankle healed and matured without further problems. In an otherwise seemingly healthy patient without vascular disease, the multiple failed wounds after multiple operations were an obvious alert to a pathergy producing pathology. Had the significance of this been appreciated after just one or two procedures, most of the prolonged activities, morbidity, expense, and remote donor sites that she went through would have been avoided.

Figures 1a, 1b are lateral and medial views of the achilles as first seen on consultation. A small area of old skin graft is mature, but most of it has villous hypertrophy or overt inflammation, with multiple small ulcers which had persisted for months. Since no skin was lost due to the original tendon rupture, all of the missing native skin was a consequence of the repetitive failed cut-and-sew procedures. **Figure 2** shows the collagen-gag matrix in place after starting warfarin and then excising the old grafts and ulcers. This resurfacing was the only one of her many prior procedures which was not complicated by wound and skin necrosis or persistent ulceration. **Figure 3** shows the result at 7 months. The skin is still immature, and there remains a small unhealed area, but there are no pathological or aberrant scar changes. **Figure 4a** is the result at 15

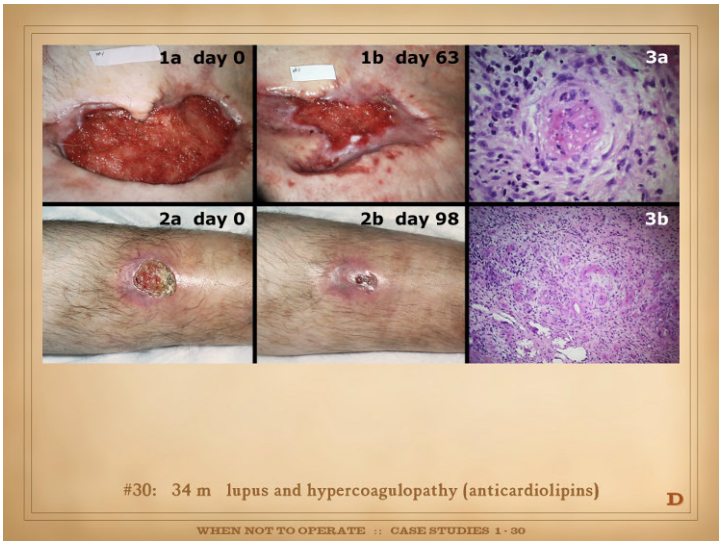
months, fully healed and maturing. **Figure 4b** is a closeup showing how the regenerated skin is thin and compliant, with Langer's lines wrinkles and creases, and with none of the scar, hypertrophy, or ulceration that was present before. **Figures 5a, 5b** confirm that ankle and skin mechanics are good. The patient has been restored to normal activities without symptoms or need for further care (except for lifelong anticoagulation).



60
Case #29
(Set 7, proscription against surgery)
Wound pathergy due to a micro-thrombotic disorder, with progressive infarcts due to repetitive surgery.

This 66 year old man had sigmoid resection for diverticular colo-vesical fistula. Anastomotic leak required drainage and colostomy, which was complicated by colonic necrosis. This was followed by colectomy and ileostomy, which resulted in small bowel infarction. With each procedure, there was progressive necrosis of the abdominal wall until most of the anterior muscles and fascias were dead. By the time of consultation, the patient was too damaged to recover. However, diagnosis of a pre-thrombotic hypercoagulable state could be established by: history (history of venous thrombosis and pulmonary embolism, and also a finger amputation for necrosis following a minor fingertip injury, a classic instance of wound pathergy); by histology (excised material showed primary small vessel thrombosis); and by laboratory (confirming activated protein C deficiency). While a simple anastomotic leak does not trigger any special diagnostic concerns, everything else in this history was an alert to a hypercoagulable or other micro-occlusive state. Unlike for skin complications, further surgery could not have been postponed in this case of peritonitis, but recognizing the problem and treating with anticoagulants would have prevented the progressive morbidity. Whenever unexpected infarcts and tissue complications occur – i.e. wound pathergy – that is the tipoff to the observant surgeon that some sort of workup and pretreatment is needed in advance of further surgery.

Figure 1 shows the abdomen after the multiple procedures described above. The deeper subcutaneous fascias are dead, and so are the muscles and muscular fascias. There are cutaneous infarcts around suture holes. The ileostomy is completely necrotic. **Figures 2, 3, 4** are specimens taken from the excised colon. There are thrombi with inflammatory infiltrates, areas of necrosis, and vascular stasis. The upper right corner in **figure 3** is the colonic lumen, ulcerated without any mucosa, with inflammatory exudates on the surface of submucosa or muscularis. The necrosis and relative low density of inflammatory cells within the tissues pegs this as a primary thrombotic event (rather than a primary inflammatory process). Acute disseminated multi-tissue vascular infarcts have few causes other than the hypercoagulable disorders. In a hypercoagulable patient, once the injury-thrombosis-inflammation triad has been upregulated into an extreme pathological attractor, it does not take much additional provocation to cause catastrophic thrombosis. It is the "flip side" of disseminated intravascular coagulation (DIC), a similar pathogenesis resulting in vascular thrombosis and infarcts rather than factor consumption and hypocoagulability. Avoiding more trauma, and giving anticoagulants and steroids are the strategies to break the cycle.



61
Case #30
(Set 7, proscription against surgery)
Wound pathergy due to an immune-coagulopathic disorder, with progressive complications of repetitive surgery.

This 34 year old man was treated for several years for systemic lupus erythematosus, controlled with steroids, but always having some level of active signs and symptoms. He sustained a small laceration on the dorsum of a finger. It did not heal after simple suturing. After other attempts at local repair, closure was tried with a full thickness graft from the groin. The groin donor wound dehisced and did not heal. An attempt was then made to close the groin wound with a fasciocutaneous flap from the adjacent lower abdomen, which likewise fell apart. The patient also had a chronic leg ulcer due to a similar minor injury over the tibia. When the first few repairs on his finger failed, especially in an area that should normally heal without problems, all in a patient with lupus, those were sufficient reasons to do no more surgery until the problems were diagnosed. When seen in consultation, the lupus was already being treated and under reasonable control. Workup was done for hypercoagulable disorders. The patient had high anticardiolipins, i.e. an antiphospholipid antibody syndrome. Warfarin anticoagulation was started, and his wounds then healed promptly by natural contraction and epithelialization supported by basic topical care. Sadly, the story does not end there. Several years later, while traveling out of town, he was in an automobile accident and required emergency laparotomy and splenectomy. Not only did his abdominal wall dehisce and fail to heal, but his transverse colon necrosed resulting in a defacto colostomy in the middle of the abdominal wound. When seen again in consultation after returning home, warfarin was restarted, along with basic wound care, and the wounds re-epithelialized. The plan was to allow the healed wounds 12-24 months to mature before taking him back to surgery for bowel and abdominal wall reconstruction. Half way into that waiting period, and no longer anti-coagulated

(the patient himself stopped taking his warfarin despite the advice for ongoing treatment), the patient tripped and fell at home. He "hurt his back". He had no immediate neurological deficits, but he became paretic over the next 24-48 hours. Imaging showed no evidence of fracture, herniation, hematoma, or other signs of cord compression. While the diagnosis could not be directly proven, it appeared that local inflammation and thrombosis in the zone of some otherwise minor musculoskeletal sprain or fracture triggered a wider zone of thrombosis that directly affected the spinal cord – an extreme but not surprising complication of the hypercoagulopathies (the same disorders that cause Budd-Chiari liver thrombosis, Paget-Schroeder subclavian thrombosis, Sheehan's pituitary apoplexy, retinal artery thrombosis, and any of the other not-so-common major thrombo-occlusive catastrophes). This syndrome of non-paretic back injury having secondary cord infarction in a patient with a an undiagnosed hypercoagulable disorder has happened in other patients as well. Anticoagulation and hyperbaric oxygen therapy were initiated, to try to minimize necrosis and salvage some function. However, given the multitude of problems that the patient faced, the family and patient opted out of further significant care. Opting for palliative care, the patient eventually died. The abdominal and spinal cord events – bizarre and unanticipated post-traumatic thrombosis and necrosis – as well as the many original skin and fascia complications, all are just another manifestation of wound pathergy, in this case due primarily to a hypercoagulable disorder, and in conjunction with an auto-immune cvd-ctd.

Figure 1a shows the groin and lower abdominal wound not long after consultation and the initiation of workup and care. It had become chronic with failed contraction and epithelialization. After diagnosis of an antiphospholipid antibody state, warfarin was started, and wound kinetics became more normal. **Figure 1b** two months later shows the response, and the wound healed entirely by continued contraction. **Figure 2a** is the tibial ulcer. It too healed readily after warfarin started, **figure 2b**. The ulceration of the finger and tibial wounds, and the necrosis and ulceration of the various flaps and grafts are all variations of post-traumatic wound pathergy. **Figure 3a** shows intravascular thrombus from a biopsy of the wound margins, consistent with the hypercoagulable disorder. **Figure 3b** shows another feature of chronic pathological ulcers typically seen in those of immunopathic and hematological origin, that of fibrinoid vessel degeneration and perivascular fibrin cuffs against a background of chronic lymphoplasmacytic inflammation – a perfect recipe for, and a forewarning of a pathergy prone state.

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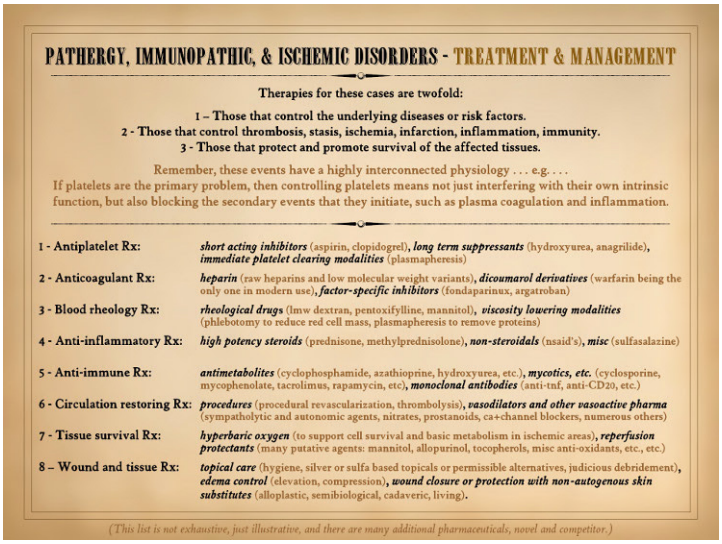
Diagnosis and evaluation of pathergy prone disorders

The ideal time to recognize and treat or preempt wound pathergy is before it happens. A proper medical history before elective surgery is the first defense against troubles. Of course, many potential pathergy problems are latent or occult, not likely to be picked up a standard first time patient encounter, especially since many of the underlying diseases might not yet have become manifest or diagnosed in a given patient. For example, as in the index case of the breast complications at beginning of this presentation, if the patient had had no other notable medical history, there would have been no compelling reason to do a comprehensive intake history for hematological disorders. On the other hand, the known history of a prior splenectomy should have raised an alert to ask about chronic secondary thrombocytosis. If the patient had no history of such, if platelet counts were normal, then further pursuit of a hematological history would have been irrelevant. In that case, since the patient did not have a history of thrombocytosis after the splenectomy, there were no problems to anticipate. That breast reconstruction was a classic case of "getting caught with your shorts down", an unexpected matter of chagrin and embarrassment that the complication happened, but it most likely could not have been anticipated or preempted.

However, once the earliest signs of trouble start, aggressive pursuit of a diagnosis and treatment of the problem can minimize the extent of damage and difficulty. For many pathergy problems, even if not anticipated in advance, once the problem is recognized, that is when to take action, forestalling further injury, settling acute pathologies, and trying to diagnose the underlying problem.

There is also a place for just knowing the rules. "Do not debride pyoderma gangrenosum". "Do not injure patients with active Behcet's syndrome." "Do not operate on someone with multiple sclerosis active or uncontrolled." "Do not close pus." "Do not amputate through a zone of ischemia." These rules serve well the surgeon and patient even when the foundational concepts behind them might not be too familiar.

Once problems occur, once a pathergy prone underlying disease is suspected, then workup is done by usual means. History and exam are crucial, looking typically for the syndromic features of vascular, hematological, coagulopathic, inflammatory, immune, and auto-immune disorders. The laboratory can be helpful in looking for confirmation of these diagnoses, or identifying particular chemical or antibody species, or evaluating quantitative severity of things as a guide to treatment. Technological tests from the vascular lab are useful very useful. Remember though that the lab has its limitations. Patients can have overt crippling rheumatoid or lupus yet still be sero-negative. Hypercoagulability can be induced by imbalances of any of the many dozens of chemicals that participate in the process, but we have interpretable tests for only about 20 of those species. When the laboratory is not diagnostic but clinical features are, then the diagnosis is made. Remember, these disorders present as multi-faceted syndromes, and for many syndromic diseases, only a portion of the relevant features need be present to have a positive diagnosis. The laboratory is just another set of features or parameters, along with those provided by history and by physical exam, and none has precedence over the others. Finally do not overlook or underestimate the value and power of the microscope. Histological evaluation of wound biopsies and debrided tissues will often reveal without equivocation what the problem or pathogenesis is. Remember though, if the wound is pathergy prone, then minimize or forestall any debridement or biopsies or incisions until proper precautions have been made for anti-inflammatory control or vascular support.



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Treatment and management of pathergy prone disorders

The treatment of pathergy risk or the event itself has several components. **(1)** Treat the underlying cause or primary diseases or risk factors. **(2)** Regardless of the disease that stirred them up, treat or control thrombosis, stasis, ischemia, infarction, inflammation, and immunity. **(3)** Start modalities that will protect and promote survival of the affected tissues.

Always remember that these events and pathophysiological stresses are all highly interconnected. Many of the pathergy prone or pathergy active events fit purely into the domain of macro- or micro-occlusive thrombo-infarction, and many fit wholly into the domain of acute neutrophilic or chronic immune lymphocytic inflammation. However, many and many more have features of both, mandating control of active thrombosis, perfusion, immunity, and inflammation, and their underlying causes, all simultaneously.

The treatments for pathergy preemption or treatment fall into several categories. Far from comprehensive listings and itemization are on the slide. The general categories include: **Anti-platelet therapies**, mostly applicable to platelet dysfunction scenarios. **Anticoagulant therapies**, applicable not just to diagnosed disorders of hypercoagulation, but as a general hedge against secondary thrombosis whenever the other categories of pathology are active. **Blood rheology therapies**, to maintain non-turbulent, non-sludging, non-thrombotic flow in vessels in various states of altered hemodynamics or disorders of the blood. **Anti-inflammatory therapies.** Just as with anticoagulation, these do more than just suppress active inflammation already established. By preempting further inflammation triggered by thrombosis and injury (always keep in mind the injury-thrombosis-inflammation triad), they keep the system from amplifying and ramping up. High potency corticosteroids such as prednisone and methylprednisolone for systemic use, triamcinolone for intralesional use, and desoximetasone for topical use are the primary tools to do so. **Anti-immune therapies** are to suppress chronic inflammation originating from lymphocytes and antibodies. Along with steroids, these are the primary tools for quenching the underlying primary diseases of immunity and auto-immunity that render the patient pathergy prone. **Circulation restoring therapies** work at macro- or microvascular levels to reestablish blood flow through altered blood vessels, often surgery for larger vessels, and pharmaceuticals at smaller scales. **Tissue survival therapies** hope to protect or cells from necrosis once the destructive events have started, such as hyperbaric oxygen in the face of ischemia, and various cytoprotective pharmaceuticals. **Wound and tissue therapies** are the more ordinary and mundane modalities that protect or prevent problems once infarction and ulceration have occurred, typically topical wound agents, edema control modalities, and skin substitutes.

All of these modalities have their role depending on the clinical scenario and diagnoses, and no clinician should be shy about using them to protect or salvage tissues in trouble. However, three of these categories are of central and crucial importance, a generic disease-independent toolbox of general purpose pathergy preventing or correcting therapeutics. Anticoagulants, anti-inflammatory therapies, and general wound and tissue therapies are the crucial armaments against pathergy. The details of which agents and how to apply them vary with each patient and situation, but categorically, these are the prime dampers to quench, arrest, or open-circuit the system once it has been triggered or gone awry into a state of pathergy-heightened auto-amplifying thrombo-infarction and inflammation-lysis.

In the acute phases of such problems, high potency corticosteroids and the heparins are the most effective and dependable and safely manageable tools to do these jobs. Any state of pathergy and active infarction and ulceration, 100%, can be arrested quickly with these modalities, preventing any more tissue loss. Whether or when a wound subsequently heals is another future chapter altogether in the management of the patient. For the moment, if active injury-inflammation-infarction-ulceration are on the rise, these tools will extinguish them. The biggest caveat is when the treating physician fails to recognize or understand the problem, fails to treat, or worse yet treats with the wrong things and provokes more trouble. This is the burden for the surgeon – do not operate on pathergy prone tissues. However, knowing how easily it is to control or preempt this risk, necessary surgery need not be delayed. Almost any such situation can be controlled by running heparin and giving parenteral and intralesional steroids at the time of surgery, be it anything from a minor biopsy or debridement to any major affair.

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How to approach surgery in wound pathergy prone cases

In wound pathergy cases, surgery must be avoided, delayed, or approached with caution and proper preparation.

Even indiscriminate debridement and biopsies carry risk.
Redo and repeat operations, especially when done not for the primary disease, but rather for consequences of the pathergy are almost certain to cause more problems

• When wound and soft tissue pathologies are present, the simple rules of "cut-and-sew" are invalidated.
• Pathergy events and complications must be explicitly and directly acknowledged and managed, not ignored.
• Without proper preparation, more surgery means more thrombosis and inflammation, augmenting the adversity.
• With explicit pathergy-oriented management, these risks and consequences are manageable and surgery can be successful.

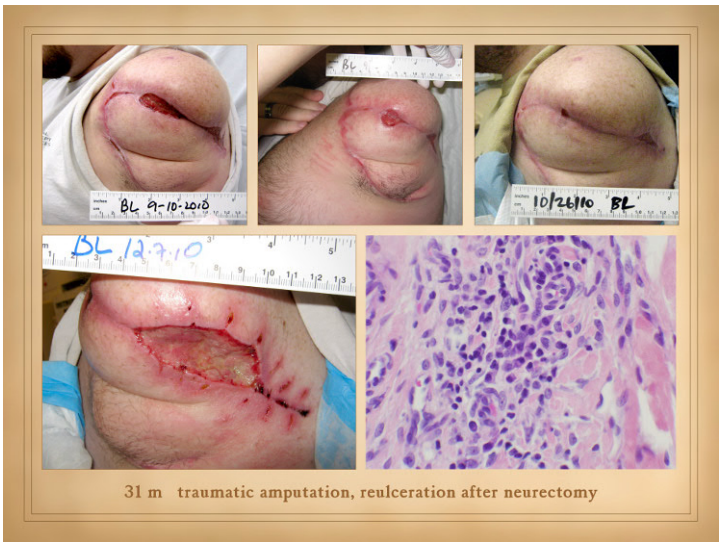
Let us return to the index case, the breast reconstruction in trouble with thrombocytosis. Below, the authors are quoted, with responsive critiques offered.

"On post-op day 18, the patient underwent operative debridement of her abdominal and chest wounds with primary closure of the breast wounds . . . over the next several weeks, the wounds deteriorated again . . ."
Never ignore the risks of wound pathergy related to hematological, immune, and related micro-occlusive disorders.
• Without proper preparation and peri-operative care, indiscriminate surgery will simply trigger more of the same.
• Recognize risks and pre-empt those risks by proper planning and treatment before the next operation.

"Over the next 2 weeks, both the mastectomy and abdominal skin flaps underwent progressive necrosis as the platelet count rose to 1390 thou/cm . . . and aspirin therapy was instituted."
No workup or therapy was done for the thrombocytosis other than aspirin.
Do not passively capitulate to the disease & its damage – take an active aggressive approach to controlling pathergy.
• For incidental thrombocytosis without problems, aspirin would have sufficed as prophylaxis against platelet complications.
• But this patient had significant complications for which repeat trouble was predictable – thorough workup & treatment were needed.
• Platelets per se are not the whole story – they trigger coagulation, then flow stasis causes more thrombosis, so anti-coagulation was needed.
• The crucial inter-relationship between platelets, thrombosis, & inflammation means that steroids should have been used.
• Hyperbaric oxygen and anti-oxidant & rheological drugs would have minimized necrosis in the ischemic flaps and wounds.
• Plasmapheresis for acute control of blood counts and viscosity, and even simple phlebotomy for hemodilution might have helped.

"Once both thrombocytosis and platelet activation occur, antiplatelet activation drugs are recommended [quote from a referenced article] . . . Should this patient ever require surgery in the future, a platelet activation profile study might be a valuable tool to assess the potential need for aggressive platelet therapy."
No, the patient needs that evaluation and treatment planning now.
This is precisely the morbid event, with life-and-limb threat, that mandates pre-emptive evaluation, diagnosis, & treatment planning:
(1) to rule out a more significant underlying problem, and
(2) regardless of specific diagnosis, to be prepared so that similar events can be prevented with future trauma or surgery.

Further studies or not, this event is now a matter of her history, and it ought to be respected and managed or preempted accordingly next time she might need surgery, even if a platelet diagnosis has not been made. Do not forget that this complication was an unexpected gremlin that jumped out of nowhere, and it might go back to sleep long before any next operation. Workup might not find the gremlin, but a surgeon would be foolish to assume that it is not there. Furthermore, if a diagnosis is not established, that does not mean that there are not ways to manage the problem. If the implication of the above quote is that they would depend on an uncertain test to do preventive therapies next time, but if the test was negative then no need to treat, then that patient is quite likely to suffer the same problem again. Remember too that many of these pathergy prone situations are due to well understand general principles of pathophysiology, e.g. there is a hypercoagulable disorder, but we do not have comprehensive or universal tests to identify all specific entities within those categories. History and exam trump blood tests, just like for the sero-negative patient who is crippled by rheumatoid arthritis. Here, the decision to treat must be based on history and good sense, not blind dependence on an uncertain test.



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Case #31
(Set 8, preparing for and preempting pathergy in surgery)
Known wound pathergy risks not managed in surgery.

This 31 year old man had amputation of the left arm just distal to the shoulder, an unsalvageable traumatic injury. The flaps and wounds healed in some areas, but not everywhere, and persistent open areas became chronic. When seen in consultation, history was negative for autoimmune, coagulopathic, and other such pathergy prone disorders. However, review of histology showed perivascular lymphoplasmacytic infiltrates. a marker of wound auto-immunization, and a marker of wound chronicity and failed healing. Miscellaneous basic therapies were undertaken, including correction of topical wound care to non-injurious agents, use of topical steroids, and avoidance of any trauma aside from perfunctory wound hygiene activities during scheduled office visits. The wounds responded quickly, all signs of pathology abated, the wound healing properly within 2 weeks. By 7 weeks, the wound was essentially healed. However, now that inflammatory pains were eliminated, the residual pains could be attributed to neuromas and neuralgias. A few weeks further on, the original surgeon did operative neurectomies. No activities were done to prevent pathergy and wound failure. Not surprisingly, the new incisions dehisced and a new chronic wound had started.

Figure 1 (top left), the problem wounds as seen at first consultation. In addition to the large central open area, various incisions have long linear open zones. Eczematous skin changes are present along the wounds and scars. Wound proliferation and granulation tissue are suppressed, and there is no epithelialization. **Figure 2** (top center), the wound just 2 weeks later. The rapid resolution of adverse findings and the onset of proper and healthy wound healing signs is dramatic, including complete closure of the long linear wounds, and substantial reduction in size of the central wound. The rapid conversion to normality suggests that faulty topical care and iatrogenic injury were the most important adverse factors, not intrinsic wound pathology. **Figure 3** (top right), 5 weeks later, shows the wound healed except for one small area where local wound geometry and skin tensions are retarding the final closure. Skin and scars otherwise look quite healthy. **Figure 4** (bottom right), despite the favorable situation after stopping faulty care and starting proper topical wound hygiene and inflammation control, biopsy done at the first visit reveals a potential wound gremlin. Perivascular aggregates of lymphocytes and especially plasmacytes are a marker of wound auto-immunization, and of the potential for wound failure. **Figure 5** (bottom left), the arm 6 weeks later after surgical neurectomies were done. Note that what has happened is not just a simple mechanical dehiscence. If so, skin edges might be apart, but the wound surfaces would otherwise look healthy and be healing. This wound instead is back to a state of pathological arrest and even active ulceration from lysis and infarction, changes which are visible along the wound edges and at the suture sites.

There is much to criticize about this. Reopening the old scars was a major faux pas, guaranteed to have this trouble. Incision through unaffected normal skin and subcutaneous fascias a few centimeters away almost certainly would have avoided any problems. Going through the problem zone afflicted by prior eczema, lymphoplasmacyte infiltrates, and confounding skin mechanics was a guarantee of failure. The need for the surgery is not in question. However, a few basic "tricks" would most likely have prevented problems. First and foremost would have been proper placement of a new incision through non-pathological tissues. If going through the same site was insisted on, then formal excision of the old scar, rather than incising through it with preservation of old memory cells, that would have helped. Simple anticoagulation, even just subcutaneous heparins would have helped. Infiltration of the surgery zone with steroids, then oral steroids afterward for a few weeks would have helped. Proper compression for mechanical support and especially edema control wound have helped, and if compression as impossible at that level, then negative pressure devices might have done the same.

Had this complication occurred totally unexpectedly in a seemingly healthy patient with no prior history and no reason to anticipate trouble, then so be it, that happens, that is the vicissitudes and reality of doing surgery on living patients with diverse problems. However, that innocent and excusable variety of trouble happened with the first go around. After all of the problems from the first set of procedures, then seeing the consultants get things healed quite easily, and knowing, or should have known because the medical records and histology were shared information, that surgeon should have taken proper precautions on the late procedure. Much of good surgery is dependent on careful fastidious cut-and-sew technique, but it is equally contingent on proper care of the non-"heal with steel" aspects of the disease. No surgery should be indiscriminate and bereft of attention to all details. However, there is a lot of latitude to challenge the body and its wounds in perfectly healthy people. That is not true in people with pathergy and wound failure risk conditions. That is especially not true in a patient who has already announced that trouble earlier in his care. This was a foolish complication for no legitimate reason.

When you know that wound pathergy and wound failure are a risk, take proper steps to prevent them.

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Wound pathergy and surgery - strategies

Surgery can be done in pathergy prone conditions. You just need to have a sensible plan, have a judicious tactical agenda about when and what to do, and do the few relevant things that will prevent pathergy, inflammation, thrombosis, infarction, and ulceration. Here are the relevant rules.

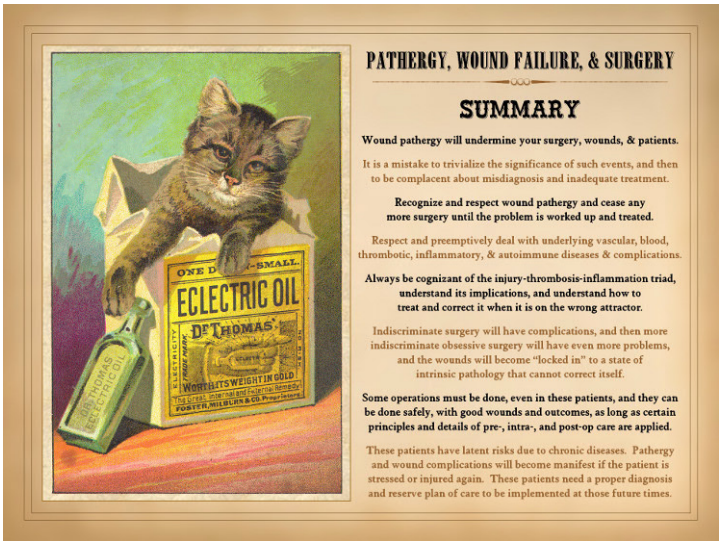
NEVER - do repair & reconstruction concurrent with drainage & debridement - NEVER. Do the debridement and wound control activities only. Then, do an interval period of good wound care, control of inflammation, management of the underlying disease if any, etc. Then, when all inflammation and disease is subsided and the wound looks healthy, then close the wound, repair or reconstruct according to what is required, the simpler the better. Doing a simple wound closure now, then coming back in 6 or 12 or 24 months for a formal reconstruction of missing or injured parts is always a virtuous strategy.

Try to anticipate, pretreat, preempt problems. When trouble happens, treat and control quickly.

Aggressively treat the underlying diseases and disorders – all patients. Treat as required with steroids and/or anticoagulants – many or most patients – be neither timid nor stingy. Ancillary Rx as appropriate for specific indications (e.g. hbo, miscellaneous pharmaceuticals, etc.)

Close with biomatrices or skin substitutes (Integra, Primatrix, Biobrane, and many others), judicious flaps, etc. Biomatrix products come out of a box and effectively close the wound without any further injury or donor sites to the host. Since circa 1996, they have proven their value as front line management to protect pathergy prone sick wounds. Avoid grafts and simple repairs. Ensure proper hygiene, topical care, and edema control for remaining open wounds.

When Surgery Must Be Done. (1) When surgery is emergent and unplanned and must be done now, then adhere to the surgery principles above, treat underlying disease, treat with steroids and anticoagulants, etc. **(2)** When surgery is mandatory and urgent but not emergent, and short preparation and planning can be done, then assess and treat state of disease or risks, and start pre- or concurrent treatment with steroids, anticoagulants, etc. **(3)** When surgery is "elective" but important, and long term planning and preparation can be done, then undertake a thorough "tune-up" of disease, then at the time of surgery, start pretreatment with steroids, anticoagulants, etc. **(4)** When surgery is non-vital or not medically indicated, then don't do it – or mind every p&q of deliberate judicious management .



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Pathergy, wound failure, and surgery - Summary

The important lessons of this review are that to avoid complications in surgery and patient care: (1) recognize and respect wound pathergy and delay or cease any more surgery until the problem is worked up and treated; (2) recognize and respect and then correct or manage a priori or active conditions of a vascular, hematological, coagulopathic, inflammatory, and immune nature.

Wound pathergy will undermine your surgery, wounds, & patients.

It is a mistake to trivialize the significance of such events, and then to be complacent about misdiagnosis and inadequate treatment.

Recognize and respect wound pathergy and cease any more surgery until the problem is worked up and treated.

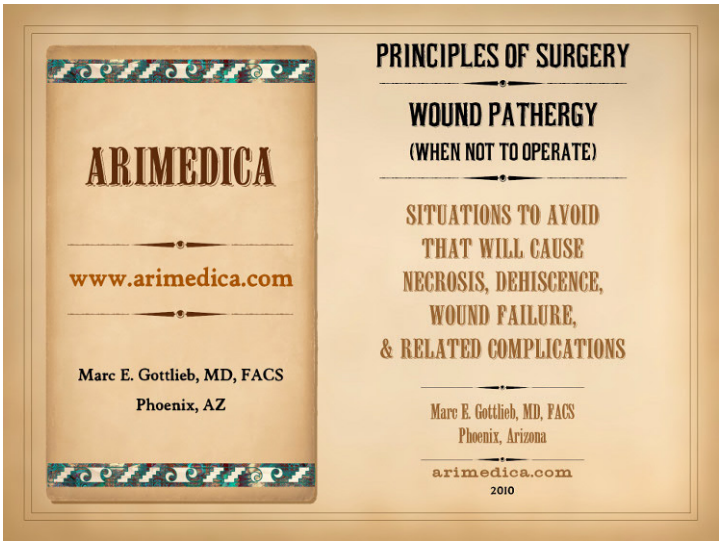
Respect and preemptively deal with underlying vascular, blood, thrombotic, inflammatory, & autoimmune diseases & complications.

Always be cognizant of the injury-thrombosis-inflammation triad, understand its implications, and understand how to treat and correct it when it is on the wrong attractor.

Indiscriminate surgery will have complications, and then more indiscriminate obsessive surgery will have even more problems, and the wounds will become "locked in" to a state of intrinsic pathology that cannot correct itself.

Some operations must be done, even in these patients, and they can be done safely, with good wounds and outcomes, as long as certain principles and details of pre-, intra-, and post-op care are applied.

These patients have latent risks due to chronic diseases. Pathergy and wound complications will become manifest if the patient is stressed or injured again. These patients need a proper diagnosis and reserve plan of care to be implemented at those future times.



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Summary

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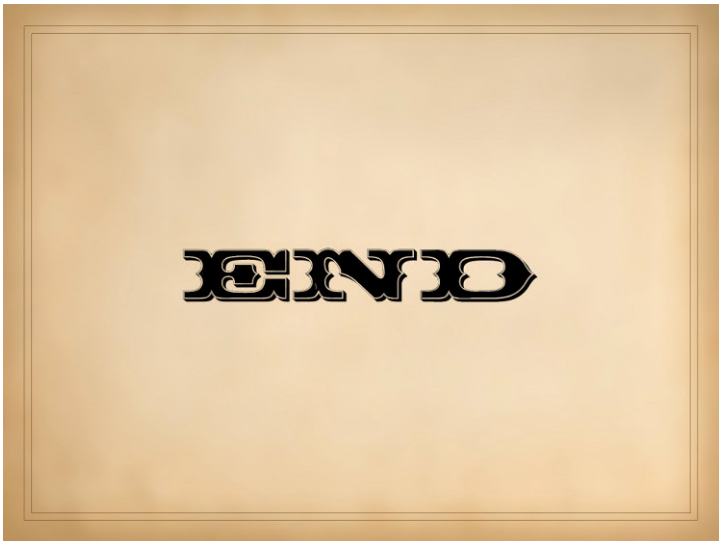

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