Malignancy as a Solid-Phase Coagulopathy: Implications for the Etiology, Pathogenesis, and Treatment of Cancer

Leo R. Zacharski, M.D.[1]

ABSTRACT

This overview of the coagulation biology of cancer is intended primarily for those unfamiliar with the link between the coagulation mechanism and neoplasia. Because the literature on this topic is extensive, citations will be primarily of previous reviews that provide detailed references. The clotting mechanism is fundamentally deranged in malignancy and, unlike the physiological hemostatic response to injury, is incapable of self-attenuation. Clotting activation may predict future cancer and the outcome of existing cancer, and participates in tumor growth. Anticoagulant therapy in patients with malignancy achieves more than control of cancer-related thrombosis. Modification of coagulation reactions relevant to particular tumor types improves the course of the disease. Viewing malignancy as a solid-phase coagulopathy provides insights into possible "upstream" causes of malignant transformation and explanations for the aberrant behavior of transformed cells and suggests innovative experimental interventions. Coagulation biology has broadened and deepened our understanding of neoplasia, and suggested testable strategies for the prevention and treatment of cancer. However, relationships between clotting and cancer progression have been established primarily from model systems. Although limited experience to date in human disease has supported these concepts, resolution of cause-and-effect relationships will require performance of additional rationally designed clinical trials.

KEYWORDS: Blood coagulation, anticoagulants, malignancy, cancer treatment

Objectives: Upon completion of the article the reader should be able to (1) explain why the coagulation-cancer interaction involves more than thromboembolic disease, (2) list several coagulation reactants capable of influencing tumor growth, and (3) appreciate the basis for the hypothesis that both coagulation activation and malignancy share primary mechanisms.

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Burgeoning interest in the link between blood clotting and malignancy has been marked by an increasing number of publications on this subject. Noteworthy characteristics of this field are its age and origin. Observations documenting the coagulation–cancer interaction span a century,[1] unless effects of leeching on cancer (possibly attributable to hirudin) are considered, in which case the span is hundreds or thousands of years.[2] This literature has been developed primarily by investigators studying the clotting mechanism rather than by oncologists. For example, the table of contents of a standard oncology textbook contains sections on every conceivable aspect of cancer biology, including hair loss and sexual dysfunction, but not on the coagulation mechanism.[3] This is startling because thrombosis is a common cause of morbidity and mortality with cancer. No information was included on coagulation test abnormalities as prognostic markers, idiopathic deep vein thrombosis (DVT) as a harbinger of subsequent cancer risk, effects of coagulation-reactive drugs on tumor progression in animal models, or effects of such drugs in clinical trials, all of which are familiar to coagulationists.[1] Perhaps anticoagulant and antifibrinolytic drugs do not seem to be antitumor agents to those accustomed to using primarily cytotoxic drugs. Perhaps coagulation activation with cancer is dismissed as a paraneoplastic phenomenon but not mainstream cancer biology. Perhaps the idea that the coagulation mechanism supports tumor growth is thought to have been disproved in the mythic past. Clarification and popularization of information on participation of the coagulation mechanism in the etiology, pathogenesis, and treatment of malignancy is needed.

Material on coagulation and cancer can be classified under three themes. First is coagulation activation in the setting of malignancy. Second is control of tumor growth by the coagulation mechanism and anticoagulants. Third is the intriguing convergence of coagulation activation and cancer inception that suggests clues to fundamental causes of both.

COAGULATION ACTIVATION WITH CANCER

Of the three themes, the first is the best developed. Although all cancer-associated coagulation activation is attributable in one way or another to transformed cells, triggering may be nonspecific or tumor cell specific.[4] Nonspecific causes include stasis due to patient immobilization; effects of damaged or necrotic normal or tumor tissues; associated inflammation or infection; entry of mucin into the circulation; effects of cancer treatment with cytotoxic drugs, radiation, and surgery; and foreign body effects of venous access devices. Tumor cell–specific causes are of two types. Tumor cells may express procoagulants, such as tissue factor (TF), that activate coagulation "directly." Alternatively, tumor cells may produce inflammatory cytokines that activate host cell procoagulant expression, for example, on macrophages or endothelial cells, thereby activating coagulation "indirectly."[4] It is informative to consider whether a given tumor type manifests direct, indirect, neither, or perhaps both mechanisms. Direct tumor cell coagulation activation within the tumor mass may explain why certain tumors exhibit tumor cell thrombin generation and are fibrin laden but systemic clotting activation is not prominent.[4] An example of such a tumor is small cell carcinoma of the lung, in which tests indicative of the degree of thrombin drive are strong prognostic indicators and reflect events taking place within the tumor.[4–6] Lymphomas have abundant tumor macrophage–associated fibrin and an intermediate risk of peripheral DVT.[4,7,8] The most prominent feature of breast cancer is tumor cell plasminogen activator rather than procoagulant activity, and, when untreated, this tumor type is associated with a relatively low risk of DVT.[8–10] In sharp contrast, indirect coagulation activation from systemic flooding with inflammatory cytokines may explain why other tumor types have dramatic, life-threatening coagulation activation with small amounts of malignant tissue (that may not have been diagnosed previously).[1] Having neither mechanism may explain why certain tumors have little associated coagulation activation.[8]

Clinical coagulopathies with malignancy take many forms, including occurrence of arterial thrombotic disease, inhibitors to coagulation factors, the "lupus anticoagulant," and so on.[1,11] Best known is DVT, which occurs clinically in up to one quarter of patients and at autopsy in about half of cases. Cancer-associated DVT may appear anywhere in the circulation, commonly recurs with or without therapy, frequently resists standard anticoagulant treatment, and marks adverse cancer outcome. Disseminated intravascular coagulation (DIC), activation of coagulation throughout the circulation, may be either compensated or decompensated.[11,12] Mild, compensated DIC, manifested only by minor changes in coagulation tests without clinical manifestations, almost always accompanies malignancy. Severe decompensated DIC that is symptomatic or represented by overt laboratory abnormalities is relatively uncommon. Depending on severity (relative production versus consumption), platelet counts and levels of individual coagulation factors may be either increased or decreased. Blood coagulation test results in malignancy mark poor patient prognosis, but associated impaired liver function, poor nutrition, medication effects, and so on confound test interpretation in individual patients. In cancer-associated coagulation activation, the ability of naturally occurring anticoagulant mechanisms to

contain unrelenting and progressive coagulation activation is overcome, the fibrinolytic mechanism is shut down, and decompensation with tissue bleeding or infarction may cause multiorgan failure. According to current concepts, subclinical DIC does not warrant treatment, but decompensated DIC may need treatment, and unfractionated heparin or low-molecular-weight heparin (LMWH) is typically used.

Treatment of DVT with malignancy presents formidable challenges (see the article by Deitcher[13] in this issue), but much progress has been made, and formal guidelines should be forthcoming in the near future. It is not known whether effects of treatment on coagulation test abnormalities might predict either disease risk or patient outcome.

CONTROL OF TUMOR GROWTH BY THE COAGULATION MECHANISM AND ANTICOAGULANTS

Although the first theme, coagulation activation with cancer, is the best developed, the second, control of tumor growth by the coagulation mechanism and anticoagulants, has the greatest potential for current clinical development. The basis for this assertion is that the coagulation mechanism is fully competent and is present on location to support tumor growth.[4] Components of coagulation reactions have been linked to aberrant behavior of transformed cells, and interventions that alter coagulation reactivity change the course of the disease.[14] Numerous drugs that intercept coagulation reactions and that have antitumor activity in experimental animal models are available for testing in clinical trials.

Framing the Coagulation Mechanism

Reflection on the design of the clotting mechanism aids understanding of how it may participate in cancer pathophysiology. Inferences from numerous bits of biochemical data (available in standard texts) on how coagulation works challenge characterization of this elegant apparatus metaphorically. Today, the traditional "cascade" or "waterfall" concepts seem pale and content deficient; a notched-up vocabulary is needed to expand our conceptual framework and nourish hypothesis generation. Table 1 offers several characteristics that intuitively seem to be more appealing expressions of the shape, strength, and usefulness of the coagulation mechanism.[15] These provide a basis for visualizing how this system might be subverted in malignancy, how the mechanism might be restored therapeutically, and perhaps the intercept responsible for carcinogenesis.

Because physiological coagulation has been picked apart to see how it works, the reverse engineering approach can be used to unpack malignancy to see what the tumor is doing to coagulation reactions, why activation is not self-attenuating, and how it might promote tumor growth.

Table 1 Molecular Characteristics of Lifeforms Exemplified by the Blood Coagulation Mechanism

Codes and codal hierarchies	Controlled algorithms
Information richness	Self-referencing
The "Wallenda" effect	Goal directedness
Integrated irreducible complexity	Sabotage susceptibility

(see text for descriptions and references)

The instructions in DNA specify the structure and use of coagulant proteins that participate in enzymatic algorithms that produce, for example, thrombin. Individual codes and algorithms are members of a hierarchy or a collection of information-rich codes, all of which are essential for the success of the mechanism. In the case of the genetic code, mutations and polymorphisms that alter the readout result in abnormal function. Postulating a link between coagulation and malignancy suggests that mutations and polymorphisms common to both might be found. Alternatively, mutations in the blood coagulation mechanism might alter expression of malignancy or vice versa. Preliminary indications suggest that this may be so.[16]

Among proteins produced by the genetic code are enzymes that direct the synthesis of other structures, such as glycosaminoglycans (GAGs) and integrins. These become participants in codes comprised of entirely different chemical symbols that have complete cooperativeness with the genetic code. For example, GAG structure imparted by these biosynthetic enzymes defines their multiplicity of functions (besides anticoagulation), including shuttling growth factors from the extracellular matrix to the cell surface to regulate cell replication on demand.[17–21] The dramatic effect of induction of subtle changes in cell-surface GAGs on tumor progression in experimental animals illustrates how important this codal hierarchy is to the economy of the malignant cell.[17]

Production of an enzyme such as thrombin would be biologically untenable without an equivalent opposing mechanism. Accordingly, the coagulation mechanism knows when and how to turn itself on and off locally to achieve the desired effect. This attribute is referred to as "self-referencing." Enzymatic activity is restrained by correction of the injury, molecules with opposing functions (thrombin is a procoagulant and an anticoagulant), and counterbalancing algorithms such as the fibrinolytic mechanism, the protein C pathway, TF pathway inhibitor (TFPI), and the activity of GAGs. This delicate counterpoise may be conceived of metaphorically as the "Wallenda effect," named after

Table 2 Comparison of Hypercoagulability due to Hereditary Thrombophilia and the Acquired Thrombophilia of Malignancy

Feature	Hereditary	Malignancy
Assumed environmental factor	Yes	Yes
Time/age-dependent onset	Yes	Yes
Increasing intensity over time	No	Yes
Site of primary reactions	Fluid phase	Solid phase
Persistence	Remitting; quiescent periods	Unremitting
Restoration with treatment	Yes	Incompletely defined

Mario Wallenda, a member of the celebrated seven-member troop that successfully navigated the high wire in generations past. Just as the high-wire artists depend on each other and are subject to falling with a falter at any one of many points, so the coagulation mechanism may falter at any one of many steps, producing bleeding or thrombosis. The dependence of each participant on the integrity of all other participants indicates that this is an "integrated irreducibly complex" system. The high wire may be likened to the surface of cells, where the "performance" occurs.

The coagulation mechanism may fail because of hereditary or acquired intercepts that produce bleeding or thrombosis. It is instructive to compare genetic thrombophilia with acquired thrombophilia of malignancy (Table 2). Although they share certain features, hypercoagulability of malignancy is unremitting and progressive. Factors acting intermittently precipitate thrombosis in hereditary thrombophilia, but there are thrombosis-free periods, especially during the first two decades of life, in spite of the genetic lesion. By contrast, with hypercoagulability of malignancy, the intercept responsible for the coagulation turn-on is ever present, and the system cannot right itself on its own, even temporarily. It is as if the intercept not only precipitates clotting activation but also blocks its compensation. It simultaneously "steps on the gas, disables the brakes, and removes the stop signs." What kind of stimulus can do this? Why is it unremitting? How is it related to the malignant phenotype? What would happen to the cancer if the primary cause of the hypercoagulability were identified and treated? Perhaps fundamental answers to these questions are hidden in data showing that certain coagulation-reactive drugs, given for even a short period of time, are capable of altering cancer outcome months or years later.[21,22]

The coagulation mechanism exists to prevent blood loss and to restore tissue architecture with injury, and its activation is attributable to the properties of injured cells. Under resting conditions, it is latent and becomes a reality only on demand. Injury sites become instantaneously colonized by members of the "swat team" that appear, act, and dissipate so rapidly that little is known about local events that initiate hemostatic plug formation or DVT in vivo. The process works well with ordinary, manageable injury. The "injury" to which the coagulation mechanism responds in malignancy does not seem to know when enough is enough. Because the "injury" persists as long as the malignancy does, coagulation reactants stay put within the solid phase coagulopathy and can be caught under the microscope lens.[4]

Cellular responses to various chemical and physical injuries ("high-wire" defects) are of two general types. One is expression of cellular procoagulants, such as TF, that trigger thrombin generation to signal activation of cells, including platelets and endothelial cells, and convert fibrinogen to fibrin.[1,4,23] Blood loss at the site of damaged vessels is prevented by forming thrombi (hemostatic plugs produced from the fluid blood). The second is expression of urokinase-type plasminogen activator (u-PA) that initiates plasminogen activation and coordinates cell proliferation and tissue remodeling, notably in organs such as the breast and kidney having secretory functions that depend on maintenance of patency of tubular structures.[4,20] This mechanism regulates clot dissolution to restore vascular patency and initiate tissue remodeling for wound healing.[4,20] It orchestrates controlled, algorithmic transformation of proteins and partitioning on cell surfaces, as well as cell proliferation, migration, synthesis, secretion, and so on. It is no wonder that elements of coagulation reactions serve as effectors of physiological processes unrelated to hemostatic plug formation, such as ovulation, fertilization, embryogenesis, organogenesis, and central nervous system function, among others. These reactions are involved in pathological processes, such as inflammation, in addition to the response to injury.[4,20] As we shall see, these reactions may be subverted to serve the deviant purposes of the neoplastic cell.

The Coagulation Mechanism and the Behavior of Transformed Cells

Coagulation reactants have not been merely implicated in the pathophysiology of cancer; they have been caught in the act.[4] Tumor masses consist of a suite of cell types,

including endothelial, inflammatory, and other cells in addition to the tumor cells. Like sites of injury, these cells are variously colonized by reactants prepared to engage coagulation algorithms and support malignant growth just as they support wound healing and tissue remodeling. Coagulant enzymes (thrombin, factor VIIa, factor Xa, factor XIIa) are also mitogens[4,23,24]; TF participates not only in coagulation initiation but also in angiogenesis[14,25]; fibrinogen and fibrin contribute in various ways, imparting cohesion and induration to the mass[4]; platelets are packets of growth factors delivered to the tumor bed[14,26]; u-PA initiates a pathway that mediates mitosis, invasion, and metastasis.[4,20,27] Among these, thrombin and u-PA seem to be the most prominent. Thrombin not only is a potent mitogen but also stimulates cell motility, angiogenesis, oncogene expression, growth factor release, extracellular matrix formation, and so on.[4,23,24] In animal models, enhanced thrombin generation increases metastatic potential, and inhibition of thrombin generation at any one of many points inhibits tumor growth and dissemination. Likewise, upregulation of u-PA expression can confer the malignant phenotype or enhance tumorigenesis, and u-PA gene transfection confers the invasive and metastatic phenotype in appropriate experimental model systems.[20,27] Correspondingly, inhibition of u-PA blocks expression of the malignant phenotype and angiogenesis.[20,27] The challenge is figuring out which pathways are relevant to which tumor types.

The reactivity of individual clotting enzymes cannot be quantified in terms of catalytic activity in solid tissue as they can be in fluid plasma, but they can be spotted visually in human malignant tissue in situ.[4] Proenzymes, cofactors, and activated intermediates can be mapped microanatomically using immunohistochemical probes that react specifically with individual proteins, with the active serine sites on factor Xa and thrombin, with thrombin–antithrombin complex neoantigen, and when the thrombin-specific cleavage sites on fibrinogen are either intact or broken (i.e., chemically defined fibrinogen and fibrin, respectively).[4] Similar techniques detect components of the u-PA pathway. Results of such studies suggested a classification of several adult tumor types based on whether the tumor cells expressed primarily a thrombin-generating pathway or u-PA.[4] Examples of tumor types having a tumor cell thrombin-generating pathway in situ include small cell carcinoma of the lung (SCCL), renal cell carcinoma, malignant melanoma, and pancreatic carcinoma.[4,28] By contrast, tumor cells in other common tumor types, such as breast, prostate, colon, and non–SCCL, express u-PA and its receptor but not a thrombin-generating pathway.[4] Quantitative studies of tissue levels of u-PA and u-PA receptor (u-PAR) antigen have shown that these are strong predictors of clinical outcome, suggesting that this "marker" also promotes disease progression in specific tumor types.[20,27] The great challenge, deciphering cause and effect, requires blocking these reactions to see what happens to the tumor.

Interventions That Alter Coagulation Reactions Change the Natural History of Malignancy

Approximately a half-century ago, experimentalists laid the foundation for numerous subsequent studies in tumor-bearing animals, showing that virtually any intervention affecting the coagulation mechanism is capable of altering malignant growth.[1] Beneficial effects of coagulation-reactive drugs included inhibition of metastasis, slowed tumor growth, increased tumor regression, and prolonged survival. A characteristic of these studies was heterogeneity in responsiveness due undoubtedly to mechanisms that varied between tumor models. Variability in response was unexplained at the time because of technological limitations. A further hurdle was that the coagulation mechanism of animals and the tumors they bear differ from the human counterparts, and results in model systems were not readily translatable clinically.

Nonetheless, progress has been made in piecing together the puzzle for human disease. Numerous studies of effects of anticoagulant drugs on human malignancy described in case reports, cohort studies, retrospective meta-analyses, uncontrolled clinical trials, and controlled prospective randomized trials have been summarized elsewhere.[21,29–31] Improved cancer outcome has been reported in certain human tumor types with drugs that interfere with thrombin-generating or urokinase-initiated pathways expressed by tumor cells. For example, SCCL appears to respond to inhibitors of coagulation (warfarin, heparin) and disruption of extracellular matrix formation.[29,32–36] By contrast, colon cancer appears to respond to inhibition of u-PA–induced plasminogen activation (aprotinin)[22] but not warfarin.[37] These studies are limited in number, and controlled clinical trials have not yet been performed in other tumor types having similar mechanisms. However, we noted that results so far correspond to the classification of tumor types described earlier based on dominant tumor cell reaction pathways in situ. No tumor type that expresses tumor cell u-PA, but not a coagulation pathway, has responded to warfarin in prospective randomized trials.[37] This classification based on mode of interaction with the coagulation mechanism may help explain the heterogeneity of results of various drug intervention studies and guide drug selection for future clinical trials. Of course, tumors in either group may share other common features, such as interaction with platelets, various heparin-binding growth factors, and pathways of new vessel formation.[14,18,19,21,25] Thus, tumors in both groups may respond to heparin that

interferes with growth factor activity, angiogenesis, or other mechanisms. Of the drugs tested so far, aprotinin and LMWH have particular appeal. The former blocks a pathway of tumor cell growth, invasion, and metastasis, and the latter may block growth factor activity, angiogenesis, and other tumor growth mechanisms as well as coagulation activation. Both seem to be remarkably effective, based on preliminary data, in human malignancy at ordinary therapeutic doses.[21,22]

To sum-up, malignancy may be conceived of as a "solid phase coagulopathy" because cells within the tumor mass engage coagulation or plasminogen activator–initiated pathways and platelets as if they were responding to injury. In contrast to physiological fluid phase coagulation activation, the consequences are played out within the tumor mass. They appear to contribute to neoplastic growth because their manipulation alters tumor cell proliferation, invasion, and metastasis and changes the course of the disease. This old idea has gained credibility as missing details have been forthcoming. Further progress can be expected as results become available from cancer clinical trials designed to target the mechanism relevant to progression of individual tumor types.

COAGULATION ACTIVATION AND THE INCEPTION OF MALIGNANCY

If the first theme, coagulation activation with cancer, is best developed and the second theme, control of tumor growth by the coagulation mechanism and anticoagulants, is currently most actively studied, the third theme may be the most tantalizing target for future investigators. Viewing malignancy as a solid phase coagulopathy prompts inquiry into the identity of the "injury" that may be the basis for both coagulation activation and carcinogenesis.

Coagulation and malignancy are intertwined from inception to death. Idiopathic DVT in an otherwise healthy individual has been a recognized harbinger of subsequent malignancy since Trousseau described the syndrome bearing his name over a century ago.[1] The risk of cancer within 2 years of diagnosing idiopathic DVT is about 10% and includes many, but not all, tumor types. High on this list are pancreatic, ovarian, hepatic, and brain tumors. Increased cancer risk persists for a quarter of a century or more after the DVT. Prandoni et al[38] followed the clinical course of 355 cases of all-cause DVT for an average of 8 years. Nine percent of patients subsequently developed malignancy, and 25% of deaths were due to cancer. The possibility exists that idiopathic DVT and malignancy might both be explained by a common intercept. Both seem to appear "out of the blue," and a common upstream cause may be concealed under the veil of passing time. Perhaps the cause has not been recognized because we have been looking the wrong way.

Clues to this unsolved riddle have come from both basic and clinical sources. For example, TF can be both an initiator of coagulation activation and a participant in an angiogenic pathway. Few, if any, normal cells express TF, but this membrane protein can be readily induced. Phorbol ester tumor promoters and the carcinogen methylcholanthrene can also initiate cellular procoagulant activity.[39,40] The arachidonic acid pathway familiar to students of platelet function has been implicated in the early stages of experimental carcinogen-induced colonic carcinogenesis.[41] Inhibition of the arachidonic acid cascade by nonsteroidal anti-inflammatory drugs (that are also antithrombotic) reverses premalignant lesions and appears to be useful for the treatment of human malignancy.[42,43] Schulman and Lindmaker[44] found that prolonged warfarin treatment for idiopathic DVT led, years later, to significantly reduced risk of urogenital (especially prostate) cancer. The drug effect seemed to be exerted in the early stages of tumor development because warfarin does not improve the natural history of established prostate cancer.[37,44] This protective effect may be explained by the anticarcinogenic properties of this class of familiar anticoagulant drugs.[45] How might these events be mediated metabolically? It should be possible to generate a short list of candidate intercepts capable of accomplishing both induction of coagulation and neoplastic transformation.

The plausibility of this construct is supported by clinical trial data showing that a relatively short course of treatment—for example, with LMWH or aprotinin—improves cancer outcome months to years later, perhaps by reprogramming the tumor cell.[17,20–22,46,47] Treating the properties of tumor cells that allow them to interact with these pathways through well-targeted therapy has obvious theoretical implications for improved patient care. This hypothesis is testable now because of the availability of new drugs having novel mechanisms of action. These include direct inhibitors of TF, factor Xa, thrombin, u-PA, and platelets; recombinant TFPI; and so on. Careful clinical trial design (matching drug mechanism with tumor mechanism and use of proper procedures for patient randomization) is required to minimize the risk of producing misleading data and reaching erroneous conclusions.[48] Incorporation of intermediate measures of efficacy into clinical trial design whenever possible should assist in determining whether the intervention is achieving the intended effect. Such intermediate measures include appropriate laboratory testing and assessment of angiogenesis through noninvasive scanning procedures, and so on. Cancer clinical trial design differs from the design of clinical trials for thrombosis prevention and treatment, and investigators are challenged to be at least as creative as the tumor.

SUMMARY

Dvorak has likened the tumor to a wound that does not heal.[49] From the point of view of coagulation biology, the conclusion is indeed inescapable that the tumor cell appears to be responding to injury by expressing procoagulants or u-PA. The advantage of viewing malignancy as a solid phase coagulopathy is twofold. First, it invites speculation on what the (as yet) invisible, time-dependent "injury" causing the "wound" might be. The coagulation mechanism is constantly receiving and transmitting information, but its capacity to respond is relatively stereotyped. If only the inciting injury could be identified and removed, the tumor might disappear or not form in the first place. Relatively few candidates exist for such a carcinogenic and coagulation-activating "injury."

Second, it provides a spawning bed for therapeutic hypotheses and appropriately designed clinical trials. It is far from clear what might be achieved should interventionists step into this information stream. However, we receive guidance from the perspective on research program development offered by design theory. The principles outlined by Gordon[50] are helpful for determining whether the coagulation mechanism regulates tumor growth and how it might do so. For example, we can begin peripherally with what we know now about normal clotting and coagulation abnormalities in cancer and work backwards to determine how it got that way (the principle of reverse engineering). This concept guided the search for coagulation reactants presumed to be assembled on cells within tumor tissues as described earlier.[4] Comparing and contrasting normal (hemostatic) and abnormal (tumor-associated) coagulation activation elucidates appropriate and inappropriate functions of the system. Continuing upstream, it should be possible to clarify how the as yet undefined intercept in malignancy subverted the beneficial coagulation mechanism, rendering it detrimental (solving the problem of dysteleology). With a clearer view of what is wrong and how abnormalities contribute to the disintegration of the whole, hypotheses on how the system can be righted acquire sharper focus.

Along the way, we must be willing to set aside preconceived notions of what the data might tell us.[45] In this regard, history has some lessons. Without the benefit of histopathology or awareness of hirudin and with only the ability to make clinical observations on a progressive disease consisting of mass lesions, Burnes described in 1812 what sounds for all the world like heterogeneity of responsiveness to chronic leeching, which was, at the time, a standard treatment for "cancer."[2] Thus

> The local bleeding is to be performed with leeches . . .
>
> Three leeches may be applied to the part every second day . . .
>
> This practice must be continued for a considerable time . . .
>
> If in the course of a month, the tumor becomes freer from pain and softer, we may apply the leeches only every third day and continue this for another month, and afterwards either persist or repeat the application at longer intervals . . .
>
> But if the tumor becomes larger, and more painful, as sometime happens . . . and if the constitution suffer by the repeated evacuations, we must desist."

We can only speculate on where we might be today had such raw observations been recorded systematically and not set aside along with the flawed hypothesis on how the intervention worked.

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