A Stress Repair Mechanism That Maintains Vertebrate Structure During Stress

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Abstract: Based on Capillary Gate Theory and Tissue Repair Theory, this paper describes the "Stress Repair Mechanism" (SRM) that maintains and repairs vertebrate tissues. It accounts for most of the mysterious manifestations of allostasis that remain unexplained by Hypothalamic-Pituitary-Axis (HPA) hormones and thereby enables the Universal Theory of Medicine predicted by Hans Selye. SRM activity explains hemodynamic physiology, capillary hemostasis, infarction, Korotkoff sounds, blood pressure, hypertension, diabetes, allostasis, allostatic load, anesthesia, analgesia, atherosclerosis, apoptosis, malignancy, eclampsia, sepsis, Multi-System Organ Failure (MSOF), the surgical stress syndrome, the fight or flight response, and numerous other manifestations of physiology and pathology. SRM function comprises the autonomic nervous system, the vascular endothelium, and the dynamic enzymatic interaction of blood-borne hepatic Factors VII, VIIIC, IX and X that produces *thrombin, soluble fibrin* and *insoluble fibrin*, whose combined effects account for all SRM manifestations. The vascular endothelium is a diaphanous neuroendocrine organ that lines all blood vessels and is the sole constituent of capillary walls. It secretes tissue factor into extravascular tissues, and insulates those tissues from the hepatic enzymes, so that tissue disruption exposes tissue factor to the enzymatic interaction and activates tissue repair. The vascular endothelium also releases nitric oxide and von Willebrand Factor into blood in accord with autonomic balance to regulate the enzymatic interaction to govern tissue perfusion and organ function. Therefore, continuously fluctuating combinations of nervous stimuli that affect autonomic balance and forces that disrupt tissues determine SRM activity.

Keywords: Stress, allostasis, allostatic load, anesthesia, analgesia, soluble fibrin, insoluble fibrin, atherosclerosis, malignancy, apoptosis.

INTRODUCTION

The ultimate objective of medical science is a Universal Theory of Medicine that explains physiology, pathology and allostasis.[1] Such a theory would enable predictably beneficial treatments and transform medical art into a genuine science. In 1954, only a year after Watson and Crick described DNA, Hans Selye utilized the Razor of Occam to postulate the presence of a physiological "stress mechanism" that repaired and maintained vertebrate tissues and would enable a Universal Theory of Medicine [1-3]. Selye's pioneering ideas established a science; introduced the concepts of *stress, stressor, eustress, distress*, and the *general adaptation syndrome*; and inspired extensive research to identify the putative stress mechanism. These efforts produced capillary gate theory and tissue repair theory; identified the coagulation cascade; clarified the relationship of Hypothalamic-Pituitary-Axis (HPA) hormones and immune system activity to stress; and established a solid body of evidence that stress induces harmful consequences in the vertebrate body that are inhibited by anesthesia and analgesia. More recently, the terms *allostasis* and *allostatic load* have supplanted Selye's classical terms. Meanwhile, interest in the field has declined due to the frustrating failure to explain tissue repair, which has led prominent experts to pronounce that no single mechanism could possibly explain the bewildering manifestations of allostasis and allostatic load [4, 5]. Nevertheless, the idea of a single mechanism has never been disproved, and its theoretical potency remains undiminished.

This paper describes the long-sought "*Stress Repair Mechanism*" (SRM) that automatically and continuously repairs and maintains the vertebrate body. The SRM was identified after new information about Factor VIII inspired an extensive review of scientific literature, enabled by Internet resources, that revealed fresh evidence for its existence and activity [6]. The distinctive physical and enzymatic properties of Factor VIII served as a "Rosetta Stone" that deciphered SRM characteristics and yielded explanations for coagulation, [7] atherosclerosis, [8, 9] capillary gate theory, [9-11] and tissue repair theory [12, 13] that were ultimately comprehended as elements of the cohesive SRM.

The SRM is strikingly similar to the old Capillary Gate and Tissue Repair Theories that enabled its identification. It consists of a *tissue repair component* and a *capillary gate component*, whose independent operations affect the dynamic interaction of hepatic enzyme Factors VII, VIII, IX and X that generates *thrombin, soluble fibrin and insoluble fibrin*, whose combined effects account for all SRM mani-

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[1]"It is the function of science to discover the existence of a general reign of order in nature and to find the causes governing this order."--Dmitri Mendeleev

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festations. The extravascular tissue repair component activates Factor VII to generate thrombin and soluble fibrin to maintain and repair tissues. The intravascular capillary gate component activates Factor VIII to generate insoluble fibrin to regulate tissue perfusion, capillary hemostasis, blood viscosity, and organ function. Because they share the enzymatic interaction, the activity of each component exaggerates that of the other to induce positive feedback that produces rapid, powerful, and focused responses to stressors. If stressors subside, the subsequent tissue repair process invokes negative feedback that restores SRM activity to maintenance levels as healing proceeds to completion. However, prolonged and exaggerated stressor activity can cause positive feedback to overwhelm negative feedback with potentially lethal consequences. Therefore, control of the SRM can improve outcome in numerous pathological conditions.

STRESS THEORY AND THE SRM

SRM activity accounts for most manifestations of allostasis and allostatic load that remain unexplained by HPA hormones (epinephrine, norepinephrine, cortisol, etc.) and immune activity. The sympathetic nervous system simultaneously activates the HPA axis and the SRM, and the SRM energizes immune activity, so that their effects are easily confused. For example, surgical stress causes an immediate increase in blood levels of HPA hormones that typically return to normal within 24 hours, while SRM effects are slower in onset, but longer lasting. It is the SRM that causes most manifestations of the surgical stress syndrome, including increases in heart disease and malignancy in the distant aftermath of surgery (see "surgical stress syndrome" on page 14) [14-18].

Allostasis is the process that enables an organism to maintain homeostasis in the presence of environmental adversity through adaptation or change [19, 20]. Allostasis is known to involve the autonomic nervous system, the HPA axis, and cardiovascular, metabolic, and immune effects that are assumed to protect the body by responding to internal and external stimuli. SRM operation explains how autonomic balance and tissue disruption affect inflammation, coagulation, hemodynamic physiology, mitosis, metabolism, chemotaxis, angiogenesis, inflammation, immune activity, atherosclerosis, tissue perfusion, and organ function [21, 22].

Allostatic Load is physiological "wear and tear" on the body that results from ongoing adaptive efforts to maintain stability (homeostasis) in response to environmental factors [23-25]. Such "wear and tear" is explained by SRM hyperactivity that produces harmful excesses of SRM products and depletes reserves of their precursors and components, which sometimes causes abnormal SRM function.

SRM activity similarly explains classical stress theory terms. *Eustress* is SRM activity that restores or enhances function. The SRM restores body structure following injury. Strength training causes the SRM to induce muscle cell proliferation and hypertrophy that increases muscle capacity [26, 27]. Endurance conditioning causes the SRM to induce angiogenesis that reduces vascular resistance, increases ejection fraction (which lowers resting heart rate), and increases exercise capacity [28-34]. *Distress* is SRM hyperactivity that exhausts Factors VII, VIII, IX and X, tissue factor, von Willebrand Factor, ATP, fibrinogen, vitronectin, and fibronectin, and produces harmful or defective excesses of thrombin, soluble fibrin, and insoluble fibrin [35-43]. Distress is synonymous with disease.

The SRM is consistent with the *general adaption syndrome* and extends it. *Alarm* is cognitive pathway activity (see "cognitive pathway" on page 12) that detects and assesses danger, chooses between fight and flight, and activates the capillary gate component *via* hypothalamic pathways (see "Capillary Gate Component" on page 6). *Resistance* is persistent positive feedback caused by unrelenting stressors that perturb hemodynamic physiology, disrupt organ function, and deplete SRM reserves of ATP, fibrinogen, vitronectin, fibronectin, and enzymes. *Exhaustion* is stressor-induced organ failure and critical depletion of SRM resources.

THE THREE SRM PRODUCTS

Thrombin is the universal enzyme of extracellular energy transduction. It transforms ATP energy into cell and enzyme activities [44-56]. Thrombin affects all cell types so far tested *via* their protease activated receptors (PAR), which vary in type and number according to individual cell types [27, 55, 57-65]. Thrombin activity requires Ca^{+}, and parathyroid glands regulate extracellular Ca^{+} to optimize its activity [26, 66-79]. Mg^{+} competitively inhibits Ca^{+} and mitigates thrombin activity [66, 75, 80-96].

The SRM continuously generates thrombin in all tissues to energize tissue maintenance [97, 98]. It accelerates thrombin generation to energize hemostasis immediately after injury [99]. It then maintains lesser thrombin elevations to energize tissue repair. As healing nears completion, it reduces thrombin to maintenance levels, causing clot disintegration and fibroblast apoptosis that facilitates wound closure [27, 61]. Thrombin energizes the following processes:

- Chemotaxis [100, 101]
- Mitosis [26, 97, 102]
- Metabolism [26]
- Hypertrophy [26]
- Angiogenesis [45, 103, 104]
- Platelet activation and thromboxane release [44, 105-108]
- Proliferation, spreading and gap formation in the vascular endothelium [109, 110]
- Release of chemokines, cytokines, interleukins, bradykinins, caspases, and prostaglandins [58, 101, 111-120]
- Production of bone, muscle, collagen and immune activity carried on by osteocytes, myocytes, fibroblasts,

and immune cells [27, 52, 68, 102, 110, 121-124, 125, 126-135]

- Conversion of fibrinogen to soluble fibrin [73]
- Conversion of fibrillar soluble fibrin to three-dimensional insoluble fibrin [72, 99, 136-144]

Older studies have confused fibrinogen, soluble fibrin and insoluble fibrin, because they are nearly identical chemically [144-148]. Their fluctuating equilibrium determines blood viscosity and coagulability (see" The Capillary Gate Component" on page 6).

Soluble fibrin is the universal protein of tissue repair. Thrombin-generated soluble fibrin leaks from the vascular system through thrombin-induced inflammatory gaps in the vascular endothelium into thrombin-inflamed extravascular tissues to form a structural matrix that facilitates tissue repair [102, 109, 149]. Soluble fibrin is the substance of pus, scabs, mucus, exudates, renal casts, and hyaline deposits [149, 150]. Its excessive production causes tissue edema, disrupts organ function, and promotes abnormal collagen production, fibrosis, sclerosis, adhesions, and scar formation [135, 146, 147, 151-160]. It resists anticoagulants and does not affect blood viscosity or hemostasis [161].

Insoluble fibrin is the universal polymer of hemostasis. Factor VIII adds plasminogen and fibronectin cross-links to fibrillar soluble fibrin molecules to generate three-dimensional insoluble fibrin that spontaneously polymerizes into strands that bind red cells and platelets together [43, 162, 163]. This binding increases blood viscosity and coagulability, accelerates atherosclerosis, activates capillary hemostasis, and forms viscoelastic clots [43, 142, 163-171]. The plasminogen cross-links spontaneously deteriorate into plasmin that disintegrates insoluble fibrin into inert fibrin split products (FSP, or d-Dimer) — unless plasminogen is continuously stabilized by thrombin *via thrombin activated fibrinolysis inhibitor* (TAFI) [141, 172-175]. Insoluble fibrin cannot escape the intact vascular system. Its generation and disintegration explains clot formation, capillary hemostasis, hemodynamic physiology, organ regulation, infarction, and the effects of anticoagulants and "vasoactive" drugs [176].

THE DYNAMIC ENZYMATIC INTERACTION OF FACTORS VII, VIII, IX, AND X

The interaction of hepatic Factors VII, VIII, IX and X generates thrombin, soluble fibrin, and insoluble fibrin. Tissue factor activates Factor VII to *initiate* the interaction [71, 140, 177-188]. Isolated Factor VII activation by tissue factor in healthy extravascular tissues continuously generates small amounts of thrombin that energize tissue maintenance, [98, 189] but are insufficient for hemostasis or tissue repair [140]. In injured tissues, Factors IX and X interact with Factor VII and tissue factor to *amplify* thrombin generation to levels that energize cellular repair activities and the conversion of fibrinogen to soluble fibrin, but are insufficient for hemostasis [140, 190]. In the immediate aftermath of injury, Factor VIII interacts with Factors VII, IX, X and tissue factor to *accelerate* thrombin generation to very high levels necessary to energize insoluble fibrin production for hemostasis [43, 142, 163, 165-171].

The priority of tissue development, maintenance, and repair is illustrated by teratogenic and potentially lethal anticoagulants and defects that affect Factors VII, X and tissue factor [56, 70, 97, 98, 123, 191, 192]. Defects in hemostasis Factors VIII, IX and XIII are non-teratogenic and survivable [193]. Heparin is non-teratogenic because it inhibits only Factor VIII.

THE CENTRAL ROLE OF THE VASCULAR ENDOTHELIUM

The vascular endothelium is a ubiquitous, diaphanous, selectively permeable layer of cells, one cell thick, that lines all blood vessels and is the sole constituent of capillary walls. It controls the dynamic interaction of enzymatic Factors VII, VIII, IX and X. The vascular endothelium secretes tissue factor hormone into extravascular tissues and then insulates it from the Factor VII flowing freely in blood, so that tissue damage exposes tissue factor to blood-borne Factor VII and initiates tissue repair component activity (see "Tissue Repair Component" on page 5) [177, 184, 187, 194-197].

The vascular endothelium also functions as a neuro-endocrine organ that releases nitric oxide hormone and von Willebrand Factor hormone into blood in accord with autonomic balance to regulate the capillary gate component (see "Capillary Gate Component" on page 6) [198-203]. Endothelial cells respond to their immediate surroundings and communicate with one another *via* electrical signals. Endothelial cells also produce fibronectin, [43] tissue factor pathway inhibitor (TFPI), [196] protein C, [204] and tissue plasminogen activator (TPA) [149, 205].

THE COMPONENTS OF THE SRM

The SRM consists of a *tissue repair component* that governs Factor VII activity in extravascular tissues, and a *capillary gate component* that governs Factor VIII activity in flowing blood. Both components share the enzymatic interaction of Factors VII, VIII, IX, and X so that the activity of each synergistically exaggerates that of the other. This explains how the SRM generates and focuses positive feedback, and produces complex manifestations.

THE TISSUE REPAIR COMPONENT

The *tissue repair component* continuously maintains and repairs tissues by elevating thrombin levels in injured tissues. It consists of the vascular endothelium, tissue factor hormone, and the enzymatic interaction of Factors VII, VIII, IX, and X.

The selectively permeable vascular endothelium allows the slow, continuous penetration of Factor VII from blood into healthy extravascular tissues, where tissue factor activates it to generate small amounts of thrombin that energize fibroblast mitosis and collagen production to maintain tissues [98, 123, 206].

Trauma disrupts the fragile vascular endothelium and directly exposes tissue factor to blood enzymes [184, 187, 207]. Factor VII activation by tissue factor *initiates* the enzymatic interaction and determines its magnitude and location [182, 183, 187]. Factors IX and X *amplify* Factor VII thrombin production to moderate levels that energize tissue repair [51, 140, 190]. Factor VIII then *accelerates* thrombin production to high levels to generate insoluble fibrin for hemostasis [54, 105, 106, 140, 208-210]. Pulsatile blood flow thrusts platelets into damaged tissues, [211] where thrombin chemotaxis attracts them and insoluble fibrin binds them into a short-lived "white clot" [106]. Thrombin-activated platelets release thromboxane that induces local vasoconstriction to temporarily reduce flow and turbulence, which increases coagulability. Rising levels of insoluble fibrin increase local blood viscosity to reduce pulsatile turbulent mixing below a threshold (see "turbulence mechanism" on page 8), whereupon insoluble fibrin binds red cells into a durable, viscoelastic, selectively permeable "red clot" that substitutes for the damaged vascular endothelium by isolating damaged tissues from flowing blood [99, 164, 171, 212, 213]. The enormous molecular size of Factor VIII prevents it from penetrating the clot and interacting with the other enzymes, so that clot formation is self-limiting.

The red clot regulates thrombin in damaged tissues [214, 215]. Factors VII, IX and X penetrate the clot and interact with tissue factor to generate thrombin, which reduces clot permeability and constrains thrombin production [53, 172, 187, 214-216]. Tissue repair then proceeds in predictable stages, energized by optimized thrombin levels [217]. Bradykinins, caspases, prostaglandins, chemokines, cytokines, and interleukins induce inflammation and enable cell-to-cell communications that coordinate cell repair activities and determine the stages of wound healing [218-222]. Inflammation loosens cell connections to facilitate the entry and movement of soluble fibrin and repair cells [109]. Soluble fibrin creates a structural matrix that facilitates repair cell activity [152]. Chemotaxis attracts fibroblasts, myoblasts, osteocytes, and immune cells into inflamed tissues, where they proliferate and produce collagen, muscle, bone, and immune activity to replace damaged tissues, inhibit infection, and remove debris and foreign substances [123, 124, 206]. Angiogenesis perfuses proliferating repair tissues. Increases in cell metabolism cause temperature elevation in healing tissues [223]. As the repair process nears completion, proliferation and spreading of the vascular endothelium restores the normal barrier between blood and extravascular tissues, which reduces thrombin generation to maintenance levels. This undermines clot integrity and repair cell viability, so that the clot disintegrates, apoptosis facilitates wound closure by actomyosin, and structural integrity is restored [57, 61, 224, 225].

The tissue repair component automatically forms abscesses, furuncles, and fistulas that isolate and expel bacteria and foreign substances. Trauma, burns, toxic chemicals, sepsis, and radiation disrupt the vascular endothelium; activate the tissue repair component, [188] and release inflammatory substances that activate the capillary gate component by stimulating its nervous sensors.

THE CAPILLARY GATE COMPONENT

The *capillary gate component* consists of Factors VII, VIIIC, IX and X, the autonomic nervous system, the vascular endothelium, von Willebrand Factor, and nitric oxide. It generates and disintegrates insoluble fibrin in accord with autonomic balance to simultaneously govern a *capillary gate mechanism* (see page 7) that regulates tissue perfusion, capillary hemostasis, and organ function and a *turbulence mechanism* (see page 8) that regulates turbulent viscosity in arterial blood flow [198, 226-228]. The capillary gate component explains why von Willebrand Factor, Factor VIII, insoluble fibrin, d-Dimer (Fibrin Split Products), blood viscosity, blood coagulability, blood pressure, cardiac output, heart rate, capillary hemostasis, tissue perfusion, tissue oxygenation, atherosclerosis, and organ function all fluctuate in accord with autonomic balance [198, 199, 228-243]. Its *acute* hyperactivation causes infarction, pulmonary embolus, thrombophlebitis, and high altitude pulmonary edema (HAPE) [41, 244-266]. Its *chronic* hyperactivation accelerates atherosclerosis and capillary senescence and causes diabetes, hypertension, and congestive heart failure [202, 228, 229, 254, 267-279].

The Factor VIII complex links the sympathetic nervous system to the enzymatic interaction of Factors VII, VIIIC, IX and X. Factor VIII consists of von Willebrand Factor produced by the vascular endothelium and Factor VIIIC produced by the liver. These bind together to circulate and exert their effects in concert. Sympathetic nervous system activity releases von Willebrand Factor hormone from the vascular endothelium to stabilize enzymatic Factor VIIIC and thereby regulate the activity and half-life of Factor VIII. Factor VIII then interacts with Factors VII, IX and X to accelerate thrombin generation to energize its conversion of Factor X to Factor XIII. Factor XIII adds "cross-links" of fibronectin and plasminogen to soluble fibrin to generate insoluble fibrin in capillaries and flowing blood [201, 280-286]. Continued Factor VIII activity inhibits the spontaneous disintegration of insoluble fibrin into inert fibrin split products *via* thrombin activated fibrinolysis inhibitor (TAFI) [137, 163, 172, 231, 287].

Parasympathetic nervous system activity disintegrates insoluble fibrin by releasing nitric oxide from the vascular endothelium. Nitric oxide is a ubiquitous gaseous signaling molecule that binds avidly to Ca+, which inactivates thrombin, and thereby accelerates the spontaneous disintegration of insoluble fibrin [203, 243, 288-298].

Capillary gate component operation requires the continuous "leakage" of tissue factor from extravascular tissues into blood circulation to activate Factor VII, without which Factors VIII, IX and X remain inert. The vascular endothelium releases Stoichiometric ATIII, tissue factor pathway inhibitor (TFPI), and protein C hormones into blood to quench excessive Factor VII activity lest Factors VIII, IX and X interact with activated Factor VII to harmfully

exaggerate thrombin generation in flowing blood [140, 175, 181, 187, 190, 196, 204, 299-304].

THE CAPILLARY GATE MECHANISM

Capillary perfusion is the essence of hemodynamic physiology. Athletic conditioning induces angiogenesis that enhances tissue perfusion and oxygenation, mitigates flow resistance, reduces blood pressure, and enhances ejection fraction, which slows heart rate *via* the Starling mechanism [28-34, 48, 270, 305-313]. Allostatic load accelerates capillary senescence, [314-316] which increases vascular resistance, impairs tissue and organ perfusion, inhibits glucose uptake, and causes diabetes and essential hypertension [148, 228, 229, 267, 273, 276, 277, 279, 317-324].

The capillary gate is a sub-microscopic, molecular mechanism that governs capillary flow, tissue perfusion, organ function, and capillary hemostasis — despite the absence of contractile musculature in capillaries [199, 251, 289, 290, 325, 326]. It operates efficiently, because capillary flow, pressure, and turbulence are minimal, and capillary surface area is greater than that of all other vessels combined. The capillary gate explains hemodynamic physiology and "vasoactive" drug effects in terms of fibrinogenesis and fibrinolysis (the generation and disintegration of insoluble fibrin) as opposed to "vasoconstriction","vasodilation" and "stiffness" of muscular arterioles that become rapidly exhausted [83, 176, 226, 233, 234, 239, 248, 251, 280, 327-331].

Sympathetic nervous system activity "closes" the capillary gate by causing the vascular endothelium cells of the capillary walls to release von Willebrand Factor [278, 282, 283, 285, 286]. This release activates Factor VIIIC, which converts fibrinogen and fibronectin at adjacent binding sites into polymerizing strands of insoluble fibrin that bind to passing red cells and halt capillary flow [43, 164, 273, 332-334].

Nitrergic neurogenic vasodilation "opens" the capillary gate by releasing nitric oxide from the vascular endothelium in visceral organs, including eye, brain, lung, GI tract, urinary tract, and pancreas *via* direct parasympathetic innervations [203, 243, 288-292, 335]. Parasympathetic stimulation also releases insulin, which indirectly mobilizes nitric oxide in the capillaries of skeletal muscle and other peripheral tissues where parasympathetic innervation is absent [328, 336-346]. This explains why insulin prolongs bleeding time, reduces systemic vascular resistance, increases cardiac index, aggravates angina, and counteracts "vasopressor" (fibrinogenic) drugs; [307, 310, 311, 329, 341, 347-350] why allostatic load inhibits insulin effects; [351] and why diabetes and hypertension are closely-related [21, 202, 228, 229, 268-271, 273, 276-279, 311-313, 317-319, 346, 352-360].

The vascular endothelium additionally regulates capillary flow *via* TPA (tissue plasminogen activator) that disintegrates insoluble fibrin, and its rapid inhibitor, plasminogen activator inhibitor (PAI-1) [205, 361-363]. Astrocytes proliferate when exposed to thrombin and release TPA to ensure brain perfusion [205, 364]. Their anticoagulant effects necessitate abundant tissue factor, which explains the exaggerated morbidity of brain injury [121, 146, 184].

Coagulopathies reveal capillary gate characteristics. Capillary structural integrity requires von Willebrand Factor, so that chronic von Willebrand Factor deficiencies cause flow-related capillary damage called *angiodysplasia* [365-373]. Sudden von Willebrand Factor destruction disrupts capillary gate structure, causing *anaphylaxis* (angioneurotic edema), wherein vascular resistance and blood pressure drop sharply as blood shifts from larger vessels into capillaries, causing lethal airway edema, while coagulation enzymes and cardiac output remain unaffected [374-376]. Defective VIIIC (true hemophilia) paralyzes capillary gate regulation, causing exercise intolerance, but capillary gate structure and anaphylaxis susceptibility remain intact [377-379].

THE TURBULENCE MECHANISM

Red cell mass greatly exceeds oxygen requirements, and hemoglobin encapsulation does not enhance oxygen delivery. However, the physical characteristics of red cells alter blood turbulence, and thereby beneficially affect blood viscosity, coagulability, atherosclerosis, and hemodynamic efficiency [380-384].

In pipes, turbulence causes viscosity (flow resistance) to increase exponentially with velocity in "Newtonian" fluids such as water and oil [385]. Mammalian blood, however, is a "non-Newtonian" fluid that exhibits exponential declines in viscosity with increasing velocity. This is because biconcave mammalian red cells spontaneously form highly efficient, self-organizing "aggregate" flow structures that suppress systolic turbulence to optimize blood acceleration, cardiac output, and peak end-systolic velocity [294, 386-392]. The resulting hemodynamic efficiency explains why the hearts of both elephant and mouse weigh only 0.6% of their body weight [393]. Diastolic deceleration disrupts the aggregates, and suddenly converts their kinetic energy into Newtonian turbulence that dissipates in a traveling pulse wave. The pulse wave periodically increases viscosity, halts flow, generates turbulent mixing that inhibits coagulation and atherosclerosis, and induces turbulent lateral forces that explain blood pressure and the palpable pulse [394, 395].

Diastolic turbulence is inversely related to red cell mass. Polycythemia accelerates atherosclerosis and increases coagulability. Anemia progressively retards atherosclerosis and paralyses coagulation [396-403].

Oil must flow through a pipeline at high rates to generate enough turbulence to prevent sludge deposits [404]. Similarly, pulsatile arterial flow operates at the threshold of peak diastolic turbulence to prevent atherosclerosis. The vascular endothelium adjusts arterial diameter *via* neuromuscular control to optimize diastolic turbulent mixing, which mobilizes particulate deposits from arterial walls [233, 405-407]. Without adequate turbulence, deposits form on the inner walls of arteries, and this activates the tissue repair

component, causing thrombin and soluble fibrin generation, inflammation, tissue factor accumulation, fibrosis, and cholesterol trapping that forms atherosclerotic plaque [197, 198, 210, 324, 408-416].

Atherosclerosis begins on the greater curvatures of arteries, where shear stress and systolic velocity decline and turbulence decreases exponentially [405-407, 417-421]. Diastolic turbulence increases exponentially with end-systolic velocity. Exercise increases cardiac contractility, elevates peak end-systolic velocity, exaggerates diastolic pulsatile turbulence, and inhibits atherosclerosis. Myxedema, congestive heart failure, and sedentary life style reduce cardiac contractility, retard peak end-systolic velocity, decrease diastolic cleansing turbulence, and accelerate atherosclerosis [3, 305, 306, 422-430].

Like ultrasound, diastolic turbulence inhibits coagulation [212]. Thrombosis is rare in arteries, where turbulence is intense, but thrombophlebitis is common in veins, where turbulence is sluggish [431]. Insoluble fibrin fluctuates in blood in accord with sympathetic nervous system activity, which is increased by allostatic load. Insoluble fibrin entangles red cells and disrupts aggregate patterns, which induces systolic turbulence that increases viscosity, decreases Ejection Fraction, and increases heart rate *via* the Starling mechanism [34, 164, 268, 391, 432]. Insoluble fibrin elevations disrupt red cell aggregates and induce turbulence during systolic acceleration that strains and collapses structurally defective red cells, causing sickle-cell anemia crisis [433-438]. Systolic turbulence also retards peak end-systolic blood velocity, which exaggerates diastolic turbulent lateral forces at the expense of turbulent mixing, elevates blood pressure, increases blood coagulability, and accelerates atherosclerosis [137, 212, 268, 384, 395, 411, 424, 439-451]. Insoluble fibrin binds red cells into a clot after it reduces turbulent mixing below a threshold [164, 212, 213].

Blood turbulence normally occurs below the threshold of hearing. Blood pressure cuff inflation constricts arterial diameter, increases flow velocity, and alters the turbulent pulse wave so as to elevate diastolic turbulent frequencies above audible levels at the distal edge of the cuff to produce *Korotkoff sounds* that are analogous to bruit sounds [452]. The blood pressure cuff measures the diastolic turbulent lateral force in arteries, as opposed to the forward force imparted by cardiac contraction that induces laminar systolic blood flow, so that blood pressure is not directly related to perfusion. Blood pressure is strikingly similar among most mammalian species because red cells and body temperature are nearly identical, and cardiac power generation is proportional to body size [393].

Hemodynamic relationships usually appear linear because turbulent variables are maintained within narrow

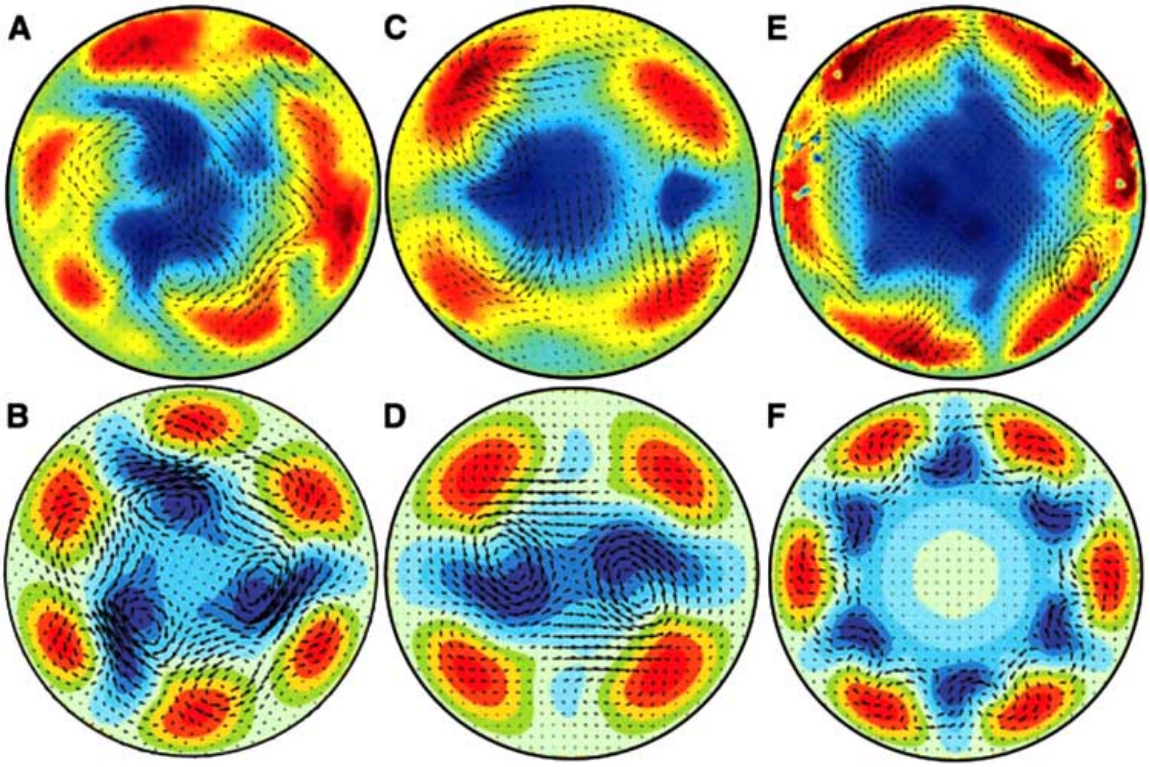

Fig. (1). Newtonian Pipe Flow Turbulence. [385] Turbulent forward flow appears as fast-moving "jet streams" (shown in red) that form along the inner walls of pipes and force slow-moving fluid to the center, where it moves *backward* (shown in blue), causing increased viscosity (flow resistance). **A**, **C** and **E** are laser photographs that show "fast (**A**), faster (**C**) and fastest (**E**)" flow acceleration that produce "small (**A**), medium (**C**) and large (**E**)" increases in turbulent intensity. **B**, **D** and **F** are computer simulations that predicted the experimental results shown by **A**, **C** and **E**. Similar arterial turbulence during diastole mobilizes particulate deposits from arterial walls to prevent atherosclerosis. It also generates lateral forces that press on the inner walls of the vessel, which explains blood pressure and the palpable pulse.

ranges. However, hemodynamic parameters are affected by complex fluctuating exponential interactions of inotropy, chronotropy, temperature, and viscosity that can produce non-linear perturbations. This explains why blood pressure and cardiac output are not linearly related [453, 454].

Reptilian red cells enhance systolic turbulence at the expense of exercise tolerance to prevent atherosclerosis caused by low temperature blood fat viscosity. Reptiles thus thrive in warm environments and their activity is sluggish at low temperatures. Mammals achieve superior exercise tolerance and dominate cold environments by maintaining their body temperature above the level of fat liquefaction, which enables their bi-concave red cells to simultaneously optimize hemodynamic efficiency and atherosclerosis resistance, but this necessitates substantially greater caloric intake [455-458].

ANESTHESIA, ANALGESIA, AND THE THREE PATHWAYS OF SRM ACTIVATION

Three independent pathways activate the SRM and focus its powerful effects: the *spinal pathway*, the *cognitive pathway*, and the *tissue pathway*. Individual stressors and combinations of stressors activate these synergistic pathways in various magnitudes, locations, intervals, and combinations, so that the manifestations of SRM activity appear chaotic and confusing. Analgesia inhibits the spinal pathway, and anesthesia inhibits the cognitive pathway. At present there is no readily available means to inhibit the tissue pathway.

THE SPINAL PATHWAY

The spinal pathway consists of peripheral nociceptors in the skin and internal organs that detect noxious stimuli and activate the sympathetic nervous system *via* peripheral nerves and internuncial spinal cord pathways [459]. Nociceptors detect vibration, temperature, and tissue disruption, but are insensitive to radiation, sepsis, and many toxic chemicals [460]. Spinal pathway activity is called *nociception*. It is modulated by cortical activity and becomes exaggerated in its absence. Analgesic agents inhibit nociception by disrupting spinal pathway activity. Various types of analgesics inhibit the spinal pathway. Cyclo-oxygenase (COX) inhibitors inactivate nociceptors. Opioids inhibit spinal cord internuncial pathways. Local analgesics such as lidocaine and marcaine block the function of peripheral nerves, spinal cord pathways, and autonomic nerve endings alike. The term "local anesthetic" is a misnomer, for local analgesics lack hypnotic effects (see Cognitive Pathway

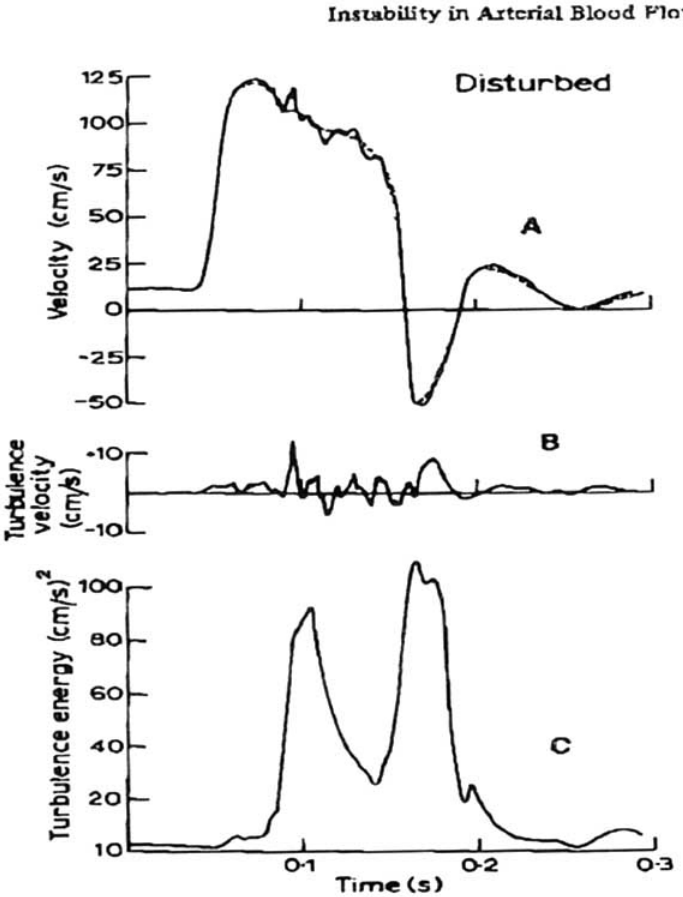

Fig. (2). Turbulence and Velocity in Pulsatile Blood Flow in a dog. Mammalian red blood cells spontaneously form aggregates that suppress turbulence during systole to enable rapid and efficient blood acceleration. Diastolic deceleration disrupts the aggregates and converts laminar systolic flow into diastolic turbulence that halts net forward flow [394]. In humans, the brief flow reversal in the distal aorta inhibits turbulent cleansing and accelerates atherosclerosis relative to the proximal aorta [408].

below). The following examples illustrate spinal pathway function:

1. Spinal Pathway nociception resists anesthesia in safe and practical doses [156, 461-466].
2. Spinal cord damage at or above the level of T5 causes *autonomic dysreflexia.* The cognitive pathway (see "The Cognitive Pathway" on page 118) no longer responds to nociception, so that pain is eliminated, but spinal pathway nociception, freed from cortical inhibition, causes harmful sympathetic nervous system hyperactivity [467].
3. Spinal cord damage below the level of T5, where cortical inhibition remains intact, synergizes the effects of general anesthetic agents in a manner analogous to analgesia by blocking spinal cord nociception pathways [468-470].
4. Analgesia prevents both nociception and pain and thereby reduces surgical morbidity and mortality more effectively than anesthesia, which prevents only pain (see Cognitive Pathway below) [16, 156, 466, 469, 471-490].
5. Fetuses and newborn babies require intense analgesia to control nociception and pain for surgical safety, but they benefit little from the addition of anesthesia, because they cannot understand language and danger, and thus lack fear and apprehension [231, 491-496].

THE COGNITIVE PATHWAY

The *cognitive pathway* consists of consciousness generated by corticofugal mechanisms that assesses environmental hazards *via* sight, sound, and nociception. It activates the sympathetic nervous system (and the HPA axis) *via* hypothalamic pathways [247, 497-501]. Consciousness interprets nociception as *pain* [265, 459, 497, 498, 502, 503]. The cognitive pathway pre-emptively activates the sympathetic nervous system in accord with combinations of pain and perceived danger (fear) [504]. The sympathetic nervous system activates the capillary gate component, which inhibits perfusion in non-critical organs and tissues such as skin and digestive system. This limits blood loss in the event of injury and concentrates blood flow in critical organs such as heart, lung and brain, whose tissues resist capillary hemostasis, and this accounts for the "fight or flight" phenomenon and also explains why epinephrine enhances outcome after cardiac arrest [505, 506]. Inhalation anesthetics are hypnotic agents that inhibit the cognitive pathway by poisoning the function of corticofugal mechanisms so as to obtund consciousness, and their effects are equivalent to those of other hypnotic agents such as benzodiazepines, barbiturates, diprivan and alcohol. Hypnotic agents inhibit pain, but have little effect on nociception. The following examples illustrate cognitive pathway activity:

1. The cognitive pathway can activate the sympathetic nervous system despite the absence of nociception. One may not sense the pain of a dentist's drill, but one can still perceive vibration, pressure, the noise of the drill, and the comments of the dentist and his staff. One anticipates pain and danger consciously, even if none is present, and this activates the sympathetic nervous system [227, 502, 504, 507, 508].
2. The cognitive pathway resists analgesia in clinically practical doses, because sight and sound remain intact. For example, spinal and epidural analgesia, analgesic block techniques, and high-dose opioid techniques for cardiac surgery often require supplementation with hypnotic agents to prevent sharp increases in blood pressure and pulse rate caused by frightening sounds and painless sensations [227, 502, 507-512].
3. Anesthesia increases surgical safety by abolishing consciousness, fear, and pain, but it cannot prevent harmful nociception in clinically practical doses [156, 461-465, 513, 514].
4. Acute emotional allostatic load, such as occurs in uninjured earthquake victims, activates the cognitive pathway and causes acute and residual elevations of von Willebrand Factor, Factor VIII, blood viscosity, blood coagulability, myocardial infarction, stroke, and blood pressure in accord with the severity of fear. This explains how people are sometimes frightened to death [24, 247, 265, 504, 509, 515-522].
5. Chronic emotional allostatic load, such as job difficulties, elevates von Willebrand Factor and Factor VIII, accelerates atherosclerosis, and shortens life span [439 500, 501, 505, 523, 524].
6. Moderate alcohol consumption inhibits consciousness and mitigates emotional distress, which reduces sympathetic nervous system activity, thus explaining its ability to inhibit heart disease and enhance longevity [227, 510-512].
7. Analgesia prevents infarction during anesthetic emergence, when the sudden restoration of cognitive pathway function and the ability to perceive pain and danger synergizes with spinal pathway nociception to harmfully exaggerate capillary gate component activity [513, 525, 526].

THE TISSUE PATHWAY

The tissue pathway consists of the vascular endothelium, tissue factor, and Factor VII. This pathway activates the tissue repair component in accord with the *magnitude* and *location* of *injurious forces* that disrupt the vascular endothelium, increase the exposure of tissue factor to Factor VII in blood, and release tissue factor into blood circulation with systemic consequences. The following examples illustrate tissue pathway activity:

1. Pneumonia and influenza insensibly disrupt the vascular endothelium in lung tissues that are rich in tissue factor, causing pathological soluble fibrin exudates that flood alveolar spaces, disrupt gas exchange, and promote collagen generation (fibrosis) [145, 149, 184, 188, 304, 527, 528].

2. Inhaled antigens imperceptibly deposit on airway passages and induce soluble fibrin generation in airway passages. This has little effect during inhalation, when airway diameters are increased, but inhibits airflow during exhalation, when airway diameters are reduced, causing asthma [529-531].

3. Bacterial products that enter the bloodstream cause sepsis by insensibly increasing the permeability of the vascular endothelium and releasing tissue factor into the blood, causing positive feedback that exaggerates thrombin and soluble fibrin generation. (See "Negative and Positive Feedback" on page 119.) Thrombin energizes inflammatory changes and soluble fibrin enters extravascular tissues, causing tissue edema and organ dysfunction [109, 147, 152, 188, 281, 532, 533].

4. brain, burn and lung injuries release large amounts of tissue factor into blood circulation, causing systemic Factor VII hyperactivity that overwhelms inhibitory mechanisms and exaggerates morbidity and mortality [146, 534].

5. Radiation cannot be detected directly by peripheral nervous sensors, but it damages the vascular endothelium and generates thrombin that energizes the release of inflammatory substances that activate tissue disruption sensors, causing belated pain.

6. Site-inactivated tissue factor neutralizes the tissue pathway [188].

NEGATIVE AND POSITIVE FEEDBACK

The *tissue repair pathway* activates the *tissue repair component* in accord with the *magnitude* and *location* of injurious forces that affect the vascular endothelium. For example, invasive surgery releases greater amounts of tissue factor into circulation than minor surgery, thereby exaggerating morbidity and mortality [14, 188, 535]. The semi-independent and synergistic *spinal* and *cognitive pathways* both activate the sympathetic nervous system, and therefore the *capillary gate component*, in accord with combinations of sight, sound and nociception. Combinations of anesthesia and analgesia synergistically inhibit sympathetic nervous system activity and control Capillary Gate Component activity.

The Tissue Repair Component *activates* Factor VII, *amplifies* thrombin production, and generates soluble fibrin [188]. The Capillary Gate Component activates Factor VIII, *accelerates* thrombin production, and generates insoluble fibrin [536]. The activity of each component exaggerates that of the other in a "chaotic" manner, [453] because both share the enzymatic interaction of Factors VII, VIII, IX and X [367, 537]. The simultaneous, synergistic activation of both components induces "positive feedback" so that peak SRM activity occurs several hours after injury [14, 15, 97, 146, 147, 538]. The constantly fluctuating activities of the three synergistic pathways enables the SRM to focus its powerful effects and generate an infinite variety of manifestations [453].

As stressors subside, "negative feedback" restores tissue repair component homeostasis *via* clot formation and vascular endothelium repair that progressively reduces thrombin production; likewise, parasympathetic activity, Stoichiometric ATIII, TFPI, TPA and protein C mobilization [299] restores capillary gate component homeostasis by inhibiting Factor VII and Factor VIII activity and accelerating the spontaneous disintegration of insoluble fibrin (see SRM diagram on page 16) [175]. However, prolonged Factor VIII half-life and spinal cord "wind up" can cause residual capillary gate component hyperactivity to linger long after stressors subside [281, 284, 488-490, 517, 539-543].

Positive feedback explains the similarities of Multi-System Organ Failure (MSOF), Adult Respiratory Distress Syndrome (ARDS), eclampsia, malignancy, and the surgical stress syndrome [147, 151, 281, 544-546]. MSOF commonly occurs after extensive injuries or sepsis, especially when both are present [135, 147, 281, 532, 547-553]. ARDS is typically the first manifestation of MSOF, because lung tissue possesses more tissue factor than other organs and is therefore affected sooner [145, 149, 151, 160, 184, 554-556]. Eclampsia is a form of MSOF that is peculiar to pregnancy, which is a form of allostatic load. Additional forms of allostatic load are invariably present in eclampsia, such as obesity, diabetes, rheumatoid disease, and urinary tract infection [150, 158, 159, 307, 557-567]. Smoking mitigates the severity of eclampsia by tranquilizing cognitive pathway activity [568].

MALIGNANCY

Malignancy is aberrant repair-cell hyperactivity caused by positive feedback that induces abnormal thrombin elevations [68, 129, 130, 223, 569-581]. It may represent re-activated embryological thrombin receptor configurations [45, 570, 581-583]. Malignant cells invade normal tissues, release tissue factor, and activate nervous sensors, causing a vicious cycle of positive feedback that sustains abnormal thrombin elevations, promotes angiogenesis, and inhibits apoptosis and resolution [121, 534, 569, 581, 584, 585]. Brain, ovary, lung, and cervix tissues that are rich in tissue factor are especially vulnerable [178, 184, 586]. This explains the close association of malignancy with allostatic load including chronic disease and environmental stressors, inflammatory symptoms, elevated Factor VII and Factor VIII activity, increased blood viscosity and coagulability, accelerated atherosclerosis, and seemingly unrelated forms of malignancy [178, 577, 587-599]. Combinations of analgesia, anesthesia, and anticoagulants that inhibit positive feedback mitigate the risk of malignancy, and improve the outcome of chemotherapy regimens [53, 97, 191, 192, 571, 600-602].

SURGICAL STRESS SYNDROME

Surgery simultaneously activates all three SRM pathways, causing positive feedback in accord with the duration and degree of sympathetic nervous system activation and tissue factor released into systemic circulation by surgical tissue disruption [14, 15, 18, 534, 603, 604]. This manifests

as symptoms distant from the location and time of surgery that are known as the surgical stress syndrome [14, 15, 17, 538, 546, 605-608]. Anesthesia controls the cognitive pathway, and analgesia controls the spinal pathway. Either anesthesia or analgesia can independently reduce positive feedback and surgical stress to the point that most patients survive surgery, [491-493, 609, 610] but outcome is further enhanced if synergistic combinations of anesthesia and analgesia are maintained continuously throughout surgery. [16, 235, 236, 325, 461, 462, 470, 491, 492, 496, 513, 514, 526, 541, 611-630]. Such combinations beneficially prevent thrombin acceleration, inhibit thrombin-induced immune activity and inflammatory effects, [631] reduce blood viscosity and coagulability, improve tissue perfusion and oxygenation, protect organ function, maintain cardiac output, reduce blood pressure, increase ejection fraction, slow heart rate *via* the Starling Mechanism and reduce the risk of malignancy and heart disease in the distant aftermath of surgery [216, 230, 235, 240, 325, 514, 612, 623, 632-651, 17]. Theoretically, the additional neutralization of tissue factor released into blood during surgery should abolish the surgical stress syndrome [184, 188, 303, 466, 494, 533].

CONCLUSION

The ability to explain disparate phenomena is the hallmark of effective theory. Tissue Repair Theory and

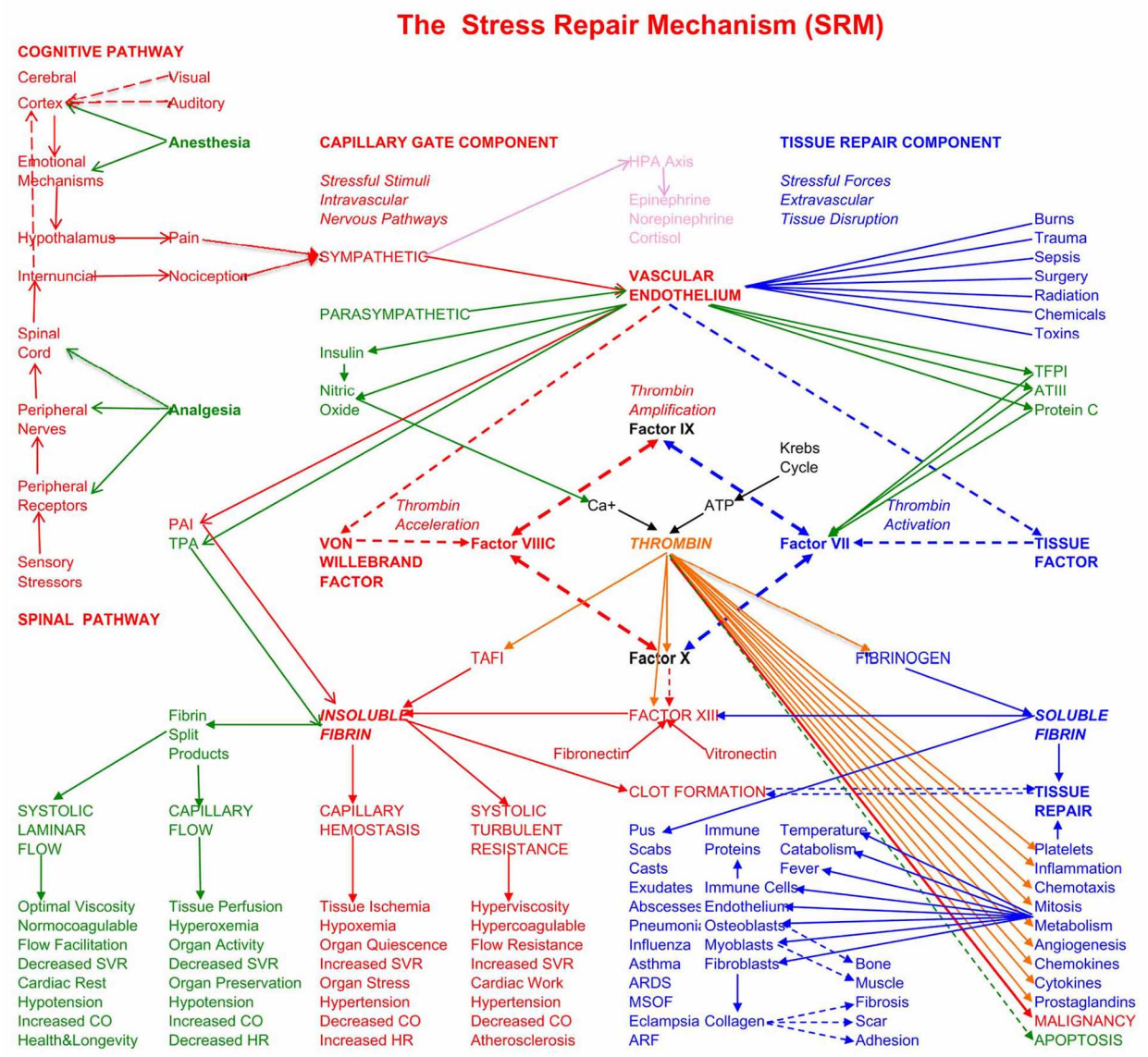

Fig. (3). The Stress Repair Mechanism. The SRM appears complex, but its underlying structure is simple and symmetrical. Arrows represent the influence (direct and indirect) that one biological function or reaction brings to bear on another. The SRM is analogous to the older coagulation cascade concept, but it combines more recent research information with capillary gate theory and tissue repair theory to explain tissue repair, physiology and pathology as well as coagulation. The capillary gate component (red) corresponds to the intrinsic pathway of the coagulation cascade. The tissue repair component (blue) corresponds to the extrinsic pathway of the coagulation cascade. Both the SRM and the coagulation cascade generate thrombin (orange), plus soluble fibrin and insoluble fibrin. Inhibitory pathways appear in green.

Capillary Gate Theory have long provided compelling but unconfirmed explanations for disease, tissue repair, and physiology. However, both had critical deficiencies, and they seemed unrelated and incompatible. Though its description remains crude due to the shortcomings of extant literature, the SRM combines both concepts and provides a detailed explanation of their function to create a cohesive explanation for presently mysterious medical phenomena. The result is a teleological marvel whose phylogeny defies comprehension. Regardless of its origin, the SRM appears to be highly conserved in nature. It suggests fresh insights to embryology and evolution as well as adult biology [652]. As long expected, it explains how DNA governs embryologic development. Its evolution might explain the Cambrian Explosion. It provides a universe of opportunities for research, diagnosis, treatment and pharmaceutical development at least as vast as current practice. If verified, it will provide the basis for the long-anticipated "Universal Theory of Medicine" that promises a new era of health, longevity, and productivity.

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ABBREVIATIONS

Term	=	Meaning
TFPI	=	Tissue Factor Pathway Inhibitor
ATIII	=	Stoichiometric ATIII
ATP	=	Adenosine Tri-Phosphate
SVR	=	Systemic vascular resistance
CO	=	Cardiac output
HR	=	Heart rate
DIC	=	Disseminated Intravascular Coagulation
HAPE	=	High-Altitude Pulmonary Edema
ARDS	=	Adult Respiratory Distress Syndrome
MSOF	=	Multi-System Organ Failure
ARF	=	Acute Renal Failure

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