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Stress repair mechanism activity explains inflammation and apoptosis

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ABSTRACT

A review of modern evidence using Internet resources has identified the Stress Repair Mechanism (SRM) postulated by Hans Selye in 1951. SRM activity regulates thrombin generation to govern tissue maintenance, tissue repair, hemodynamic physiology, inflammation, and apoptosis. Thrombin utilizes ATP to energize coagulation, capillary hemostasis, chemotaxis, immune activity, mitosis, metabolism, angiogenesis, and the release of chemokines, cytokines, bradykinins, and prostaglandins that enable cell-to-cell communications, promote perfusion, loosen cell connections, and sensitize nociceptors during tissue repair. The orchestration of these diverse activities by the SRM explains the disparate elements of the inflammation syndrome, including dolor (pain), rubor (redness), calor (heat), tumor (swelling), and Functio laesa (loss of function). Inflammation resolves as tissue repair nears completion and declining SRM activity restores thrombin to maintenance levels. As thrombin levels decline below a critical threshold, repair cells undergo apoptosis and clots disintegrate. Apoptosis shrinks granulation tissues to enable wound closure. Apoptosis also facilitates embryological development. Occult systemic SRM hyperactivity due to sepsis, surgery, trauma, chemicals, pain, fear, and emo-tional memories causes inflammatory effects that manifest as the fever, edema, malignancy, organ disruption, eclampsia, Multi-System Organ Failure (MSOF), Systemic Inflammatory Response Syndrome (SIRS), Adult Respiratory Distress Syndrome (ARDS), Disseminated Intravascular Coagulation (DIC) and other pathologies.

Keywords: Selye; Stress; Inflammation; Atherosclerosis; Tissue Repair; Hemodynamic

1. INTRODUCTION

Medicine remains an art based on experiment rather than a true science based on theory that enables predictably effective treatments. The nature of tissue repair is unknown. Inflammation, apoptosis, and embryological development remain mysterious. Hemodynamic physiology is customarily attributed to direct autonomic innervation that controls cardiac and arteriolar contractility, but this explanation is notoriously weak. Smooth muscle contraction is energy intensive, short-lived, and followed by obligatory vasodilation, so that it cannot explain sustained hypertension. Sustained increases in cardiac work cause congestive heart failure. These and other shortcomings in medical theory force physicians to base their treatments on symptoms rather than causes, so that treatments are often useless or even counterproductive.

Stress theory has represented the best hope for improved medical theory in recent times. In 1951, Hans Selye famously predicted that a single physiological mechanism maintains and repairs the vertebrate body. Selye's putative mechanism would theoretically enable a "Universal Theory of Medicine" that explains hemodynamic physiology, tissue repair, pathology, stress, and their relationships. It would revolutionize medical treatments and pharmaceutical development. Soon after Selye's prediction, the discovery of DNA inspired enormous excitement in medicine and biology. Since the DNA mechanism by itself does not explain how genetic information is converted into structural development, many expected that Selye's mechanism would function as a "companion mechanism" that works closely with DNA to enable embryological development. The companion mechanism would remain active to maintain mature structures and regulate hemodynamic physiology for the duration of life, while DNA becomes quiescent once embryological development is complete. These exciting ideas inspired an intense but futile international search for a testable mechanism that could confirm Selye's theory.

Stress researchers developed two important concepts to help identify Selye's mechanism. *Capillary gate theory* postulates a submicroscopic mechanism that effi-

ciently controls capillary flow. It theoretically explains capillary hemostasis, hemodynamic physiology, and organ function. *Tissue repair theory* postulates a single mechanism that governs tissue repair. It theoretically explains the orderly and predictable sequence of events that occurs during tissue repair, including inflammation and apoptosis [1].

Stress research lasted more than 30 years and consumed hundreds of research careers, thousands of test animals, and millions of dollars. Unfortunately, no testable mechanism was found that explains tissue repair or hemodynamic physiology, let alone both. Furthermore, capillary gate theory and tissue repair theory seemed incompatible. Despite its promise, the frustrating failure to find a testable stress mechanism caused stress theory to fall into disrepute, and it has now been almost completely abandoned for more than 30 years. Prominent experts have pronounced that no single mechanism could possibly explain the bewildering multitude of stress and disease manifestations [2,3]. However, that turns out not to be the case.

Powerful scientific theories often appear long before their time. They must await the death of critics and the accumulation of supporting evidence before they are embraced, and the visionaries who contribute them seldom outlast their critics[1]. Nearly thirty years after Selye's death, fresh evidence has finally enabled the first description of the long sought "*stress repair mechanism*" (SRM) that explains stress theory and enables it to be tested and verified (**Figure 1**) [4]. The SRM was identified after compelling new information about coagulation factor VIII inspired an extensive review of scientific literature using Internet resources [5]. PubMed provided the primary source of published medical research reports. Computer search techniques made it possible to efficiently evaluate thousands of research abstracts to identify pertinent papers, and obtain full copies via email. Sophisticated "Endnote" software[2] facilitated the management of hundreds of essential references. The distinctive physical and enzymatic properties of factor VIII served as a "Rosetta Stone" that deciphered SRM characteristics and yielded a fresh explanation for coagulation [6] that was soon followed by explanations of atherosclerosis [7,8], capillary gate theory [9,10], and tissue repair theory [11,12]. Finally, all of these seemingly disparate mechanisms were comprehended as elements of the SRM [4].

The SRM exceeds the expectations of earlier stress researchers. As they anticipated, it explains both hemodynamic physiology and tissue repair, and it enables Selye's Universal Theory of Medicine that explains physicology, pathology, stress, and their relationships. In addition, it provides a new theory of anesthesia, analgesia, allostasis, and surgical stress [13]. Its appearance explains the Cambrian Explosion. It provides unexpected insights to vertebrate cell biology, embryology, evolution, anatomy, apoptosis, behavior, intelligence, and taxonomy that will be detailed in a future publication. It explains the hitherto mysterious nature of inflammation and apoptosis and their role in the tissue repair process, which is the subject of this paper.

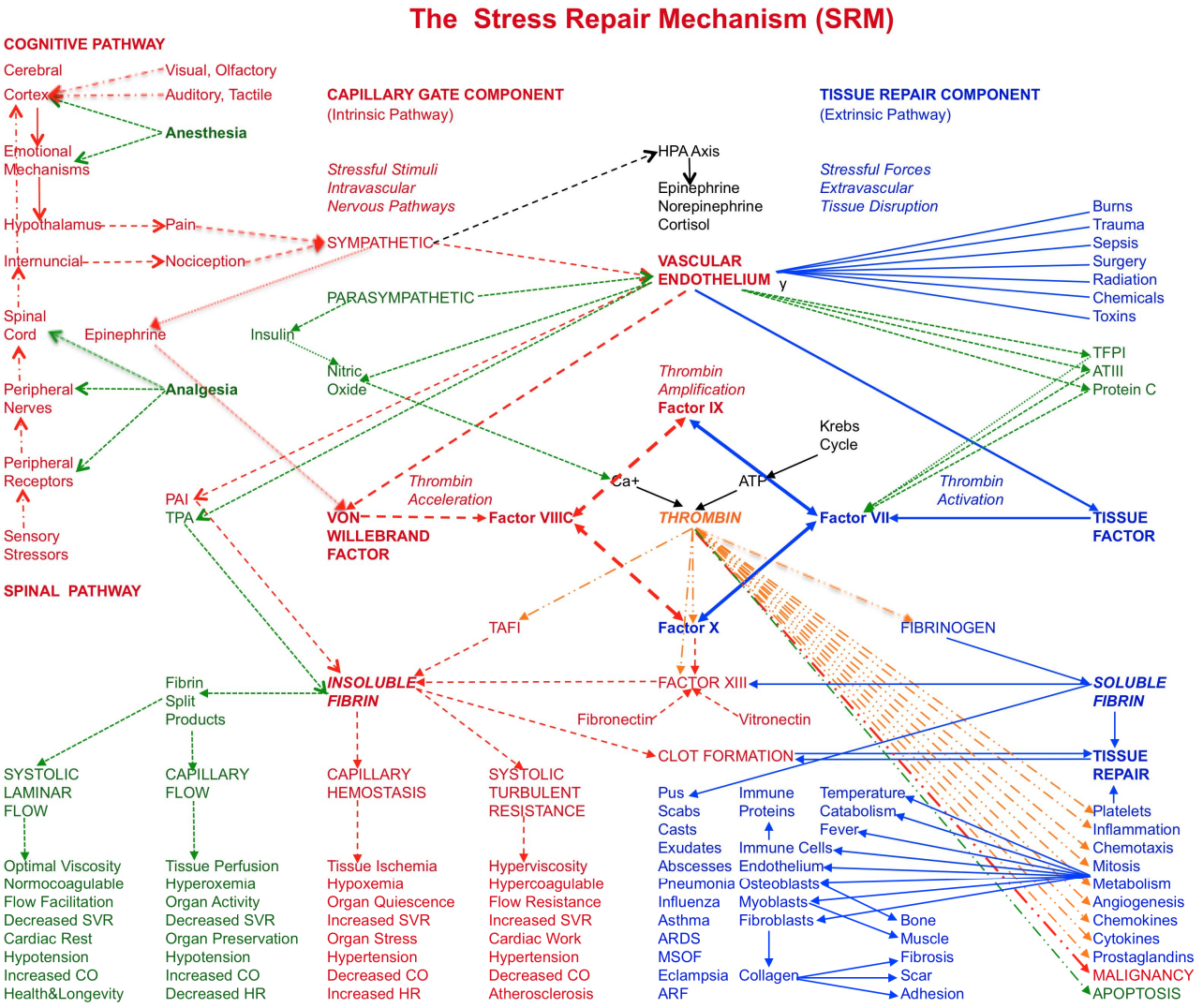
It retrospect, it is not surprising that the SRM eluded detection until now. It is complex and counterintuitive, and it conflicts with entrenched medical beliefs, practices, and assumptions. In retrospect, the previous generation of stress researchers was amazingly insightful, and their capillary gate and tissue repair theories paved the path to SRM discovery. The "coagulation cascade" concept that appeared in their time was analogous to the SRM, but critical information necessary to clarify the relationships of coagulation enzymes to tissue repair was unavailable until recently. Apoptosis was generally unknown before 1972 [14]. The dual autonomic innervation of the vascular endothelium was unclear [15]. Thrombin was regarded as a "coagulation enzyme" that was similar to other enzymes in the coagulation cascade. The chimeric nature of Factor VIII had yet to be clarified [5]. "Nitrergic Neurogenic Vasodilation" was unknown [16]. Chemokines and cytokines were obscure [17]. Chemical tests could not distinguish the physical properties of fibrinogen, soluble fibrin, and insoluble fibrin. These and other important elements of SRM operation have been clarified during the 30 years since stress theory was abandoned, and this fresh information has finally enabled the first crude description of the SRM.

2. THE STRESS REPAIR MECHANISM

Even though compelling evidence suggests an intimate relationship between coagulation and tissue repair, medical education has traditionally treated hemostasis as an independent phenomenon whose sole purpose is to stem blood loss. Researchers and clinicians may therefore be surprised to learn that coagulation is but one manifestation of the cohesive SRM mechanism that explains tissue repair, hemodynamic physiology, pathology, and stress. Detailed and fully referenced descriptions of the SRM and its medical effects have already been published [4, 13] and are available from the author's website[3].

The SRM consists of the autonomic nervous system, the vascular endothelium, and the enzymatic interaction of blood-borne hepatic enzyme Factors VII, VIII, IX, and X that generates thrombin, soluble fibrin, and insoluble fibrin. The effects of these three products explain all SRM manifestations, including inflammation and apoptosis.

[1] http://en.wikipedia.org/wiki/Alfred_Wegener
[2] http://www.endnote.com/enhome.asp
[3] www.stressmechanism.com



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
TPA	Tissue Plasminogen Activator
PAI	Plasminogen Activator Inhibitor

Figure 1. The Stress Repair Mechanism (SRM). 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 produce a cohesive explanation of capillary hemostasis, tissue repair, physiology, and pathology as well as coagulation. The capillary gate component corresponds to the intrinsic pathway of the coagulation cascade. The tissue repair component corresponds to the extrinsic pathway of the coagulation cascade. Both the SRM and the coagulation cascade generate thrombin, and convert fibrinogen to soluble fibrin and thence to insoluble fibrin.

Thrombin is the "Universal Enzyme of Extracellular Energy Transduction." Though it is conventionally regarded as a "coagulation enzyme," it energizes both hemostasis and tissue repair. It also energizes activity that is not directly related to SRM operation, such as the complement cascade and gelsolin [18,19]. It transforms ATP energy into both cell and enzyme activities [20-32]. It affects all cell types thus far tested via their protease activated receptors (PAR), which vary in type and number according to individual cell types [31,33-42]. It increases intracellular Calcium levels and mitochondrial activity via PAR-1 receptors [21,31,37,43-48]. Its activity requires Ca+, and parathyroid glands regulate extracellular Ca+ to optimize its activity [48-62]. Mg+ competitively inhibits Ca+ and mitigates thrombin activity [46,49,58,63-78].

All cells thus far tested possess PAR (thrombin) receptors that are present in various combinations that are characteristic of specific cell types, and these combinations determine how individual cell types react to thrombin [79,80]. PAR (thrombin) receptors are over-expressed during both malignancy and normal tissue repair [25,81].

The SRM continuously generates thrombin in all tissues to energize tissue maintenance [82,83]. It accelerates thrombin generation to energize hemostasis immediately after injury [84]. It then maintains lesser thrombin elevations to energize tissue repair [79]. As healing nears completion, it returns thrombin to maintenance levels, causing clot disintegration and apoptosis of repair cells that facilitates wound closure [33,38]. Thrombin energizes and orchestrates all elements of tissue maintenance and repair including the following:

- Chemotaxis of platelets, osteocytes, white blood cells, and other tissue repair cells [53,79,80,85]
- Mitosis [42,53,82,86,87]
- Metabolism [53]
- Hypertrophy [53,80,88-91]
- Angiogenesis [21,45,92]
- Platelet activation, chemotaxis, and thromboxane release [20,93-96]
- Proliferation, spreading and gap formation in the vascular endothelium [47,97]
- Release of chemokines, cytokines, interleukins, bradykinins, caspases, and prostaglandins [35,85,90,98-106]
- Production of bone, muscle, collagen and immune activity by osteocytes, myocytes, fibroblasts, and immune cells [17,28,33,43,51,80,86,89,91,97,107-116]
- Conversion of fibrinogen to soluble fibrin [56] that facilitates tissue repair
- Conversion of fibrillar soluble fibrin to three-dimensional insoluble fibrin [55,84,117-125] that enables hemostasis and regulates tissue repair and hemodynamic physiology
- Stabilization of insoluble fibrin via "Thrombin-Activated Fibrinolysis Inhibitor" (TAFI) [122,126-129]
- Inflammation, which dissolves the "basement membrane" that binds cells in tight formation with one another and with the Vascular Endothelium to facilitate chemotaxis [37,51]
- Proliferation of astrocytes and glial cells in brain tissue [42,87].
- Activation of gelsolin that neutralizes Actin [18]
- Complement activation that attacks foreign antigens [19]
- T-cell activation independent of an immune response [39,109]
- Blast transformation in lymphocytes
- Increased macrophage phagocytic activity [39,45,48, 92,109,113,130]
- Activation of plasma (immune) cells and neutrophils [113,124,131]
- Release of "Tumor Necrosis Factor" from microglial cells [132]
- Tumor growth, malignancy, and fibrosis [29,33,34,38, 107,108,112,133,134]
- Inhibits apoptosis [31,34,40,41,135,136]
- Intracellular gap formation in the vascular endothelium that increases permeability [47]
- Defects in Factors VII, X and Tissue Factor that disrupt thrombin generation necessary for embryological development and tissue repair are generally lethal [137]
- Embryological development, tissue maintenance, wound healing [24,44,82,83,138]

Thrombin energizes the conversion of fibrinogen to soluble fibrin, and then energizes the conversion of soluble fibrin to insoluble fibrin (see below). Older studies have confused fibrinogen, soluble fibrin, and insoluble fibrin, because they are nearly identical chemically [125, 139-142]. Their fluctuating equilibrium determines blood viscosity and coagulability (see "The capillary gate component" below).

Fibrinogen is a structurally complex protein molecule that exists in more than one form. It is the precursor of both soluble and insoluble fibrin. The liver produces and releases fibrinogen into the blood at steady rates. It cannot escape the intact vasculature. It is not directly involved in either tissue repair or hemostasis, but fibrinogen depletion causes defective insoluble fibrin production [117,143]. Fibrinogen consists of alpha, beta and gamma subunits that are connected by disulfide bonds [125]. Thrombin disrupts the disulfide bonds and causes the alpha, beta, and gamma fibrinogen subunits to polymerize into fibrillar (two-dimensional) strands of "soluble fibrin" [47,56,123].

Soluble fibrin is the "Universal Protein of Tissue Repair." It is the precursor of insoluble fibrin, but it has no

direct effect on blood viscosity and coagulability. It is the substance of pus, scabs, mucus, exudates, renal casts, and hyaline deposits [144,145]. Thrombin-generated soluble fibrin escapes 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 the formation of granulation tissue that fills wound cavities [28,47,56,86,122,124, 144]. Excessive soluble fibrin generation causes tissue edema and disrupts organ function. For example, soluble fibrin causes proteinuria and hyaline casts. It disrupts pulmonary function by flooding alveoli in pneumonia and influenza, and narrowing airway passages in asthma [139,144,146,147]. Soluble fibrin deposits promote collagen production, fibrosis, sclerosis, adhesions, and scar formation [116,140,141,148-159]. For example, peritoneal soluble fibrin deposits produce peritoneal adhesions after surgery and infection, and alveolar soluble fibrin evolves into pulmonary fibrosis in the aftermath of ARDS, chronic asthma, and prolonged pulmonary infection. Thrombin inhibition mitigates soluble fibrin generation and collagen production [108], but most anticoagulants have minimal effect on soluble fibrin deposits and collagen scars once they have formed [160].

Insoluble fibrin is the "Universal Polymer of Hemostasis". It cannot escape the intact vascular system. It binds red cells and platelets together, and this produces several seemingly unrelated effects. It increases blood viscosity and coagulability, accelerates atherosclerosis, activates capillary hemostasis, and forms viscoelastic clots that stem blood loss and then regulate tissue repair [123,161-170]. The generation and disintegration of insoluble fibrin explains viscoelastic clot formation, capillary hemostasis, hemodynamic physiology, organ regulation, tissue repair regulation, atherosclerosis acceleration, infarction, and the effects of anticoagulants and "vasoactive" drugs [171].

The conversion of soluble fibrin to insoluble fibrin occurs in a series of complex enzymatic interactions. Factor VIII accelerates thrombin generation to energize its enzymatic conversion of Factor X to Factor XIII [163, 168,169]. Factor XIII adds plasminogen and fibronectin cross-links to fibrillar soluble fibrin to generate three-dimensional insoluble fibrin that spontaneously polymerizes into strands that bind red cells and platelets together [165,170,172]. 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) [122,126-129]. Parasympathetic Nervous System (PNS) activity stimulates the release of nitric oxide, which binds avidly to Ca+, inactivates thrombin, and accelerates the disintegration of insoluble fibrin [49]. The effects of insoluble fibrin are thus readily reversible, and this explains the fluctuations of blood viscosity, tissue perfusion, and organ regulation in accord with autonomic balance.

Hemophilia and von Willebrand Disease Coagulopathies illustrate the difference between soluble fibrin and insoluble fibrin. Both conditions paralyze Factor VIII, which impairs the ability to convert soluble fibrin to insoluble fibrin for hemostasis. Afflicted patients retain the normal ability to generate soluble fibrin to repair tissues and produce pus, scabs, exudates, soluble fibrin deposits, fibrosis, scars, and adhesions [173,174]. Like normal patients, they produce excessive quantities of soluble fibrin in accord with pneumonia, influenza, ARDS, MOFS, asthma, and eclampsia [146,147,155-157,175]. However, their inability to produce Factor VIII in normal quality and/or quantity inhibits their ability to accelerate thrombin generation to activate platelets, energize the enzymatic conversion of soluble fibrin to insoluble fibrin, and stabilize the insoluble fibrin molecule via "Thrombin-Activated Fibrinolysis Inhibitor" (TAFI) [93,126,170, 176-182]. This explains why they exhibit abnormally low blood viscosity and coagulability, retarded atherosclerosis, and reduced incidence of heart disease, as well as defective coagulation and capillary hemostasis [183-185]. Defects or deficiencies in Factor XIII also disrupt the conversion of soluble fibrin to insoluble fibrin by inhibiting the installation of plasminogen and fibronectin cross-links in the insoluble fibrin structure, but these Coagulopathies do not impair thrombin generation and platelet activation and are usually less severe [186-188].

Insoluble fibrin elevations cause increased viscosity and coagulability that pre-disposes to Disseminated Intravascular Coagulation (DIC), thrombophlebitis, pulmonary embolus, and accelerated atherosclerosis [189-194]. Insoluble fibrin generation also closes the capillary gate and disrupts perfusion and oxygenation in organs and tissues (see "Capillary Gate Component" below). This causes stroke [195,196], mental disturbances [197,198], myocardial infarction [195,199-202], renal dysfunction [145], bowel infarction, bowel ileus, and increased vascular resistance.

3. 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 [54,121,158,203-213]. Factor VII slowly penetrates the vascular endothelium to enter extravascular tissues, where tissue factor activates it to generate small amounts of thrombin sufficient to energize tissue maintenance [83, 214], but insufficient for hemostasis or tissue repair

[121]. 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 coagulation [123,162-170]. The viscoelastic clot then regulates contact between blood enzymes and damaged tissues. It is impermeable to Factor VIII, but it allows Factors VII, IX and X to enter damaged tissues, where Factors IX and X interact with Factor VII and tissue factor to *amplify* thrombin generation to levels sufficient to energize cellular repair activities [121,215].

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 [32,52,82,83,108,216,217]. Defects in hemostasis Factors VIII, IX and XIII are non-teratogenic and survivable [173]. Heparin does not disturb tissue maintenance and is non-teratogenic because it inhibits only Factor VIII.

4. 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 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” below) [203,210,212,218-221].

The vascular endothelium also functions as a neuroendocrine 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” below) [15, 222-226]. Endothelial cells respond to their immediate surroundings and communicate with one another via electrical signals. Endothelial cells also produce *fibronectin* [165], *tissue factor pathway inhibitor* (TFPI) [220], *protein C* [227], and *tissue plasminogen activator* (TPA) [144,228].

5. THE SRM SUB-COMPONENTS

The SRM consists of two semi-independent sub-components. The *tissue repair component* regulates Factor VII activity to maintain and repair extravascular tissues. The *capillary gate component* regulates Factor VIII activity to govern hemodynamic physiology. These two sub-components share the enzymatic interaction of Factors VII, VIII, IX, and X, so that the activity of each exaggerates that of the other. This enables the SRM to generate positive feedback and focus its powerful effects to repair damaged tissues. It also explains the bewildering variety of SRM manifestations in health and disease.

6. 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 9) that regulates tissue perfusion, capillary hemostasis, and organ function and a *turbulence mechanism* (see page 10) that regulates turbulent viscosity in arterial blood flow [222,229-231]. 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 [15,222,231-246]. Its *acute* hyperactivation causes infarction, pulmonary embolus, thrombophlebitis, and high altitude pulmonary edema (HAPE) [189,190,195,199,247-266]. Its *chronic* hyperactivation accelerates atherosclerosis and capillary senescence that causes diabetes, hypertension, and congestive heart failure [225,231,232,257,267-279].

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 [224,280-286]. Continued Factor VIII activity inhibits the spontaneous disintegration of insoluble fibrin into inert fibrin split products via thrombin activated fibrinolysis inhibitor (TAFI) [118,126,170,179, 234].

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 [16,226,246,287-296].

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 [121,129,201,207,212,215,220,227,297-301].

7. 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 [24,270,302-317]. Allostatic load accelerates capillary senescence [318-320] that increases vascular resistance, impairs tissue and organ perfusion, inhibits glucose uptake, and causes diabetes and essential hypertension [142,192,231,232,267,273,276,277,279,321-327].

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. [15,254, 288,289,328,329] 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 disintergration of insoluble fibrin) as opposed to "vasoconstriction," "vasodilation," and "stiffness" of muscular arterioles that become rapidly exhausted [66,171,229, 236,237, 242,251,254,280,330-334].

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 [161, 165,186,273,335,336].

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 innervation [16,226,246,287-290,337]. 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 [331,338-348]. This explains why insulin prolongs bleeding time, reduces systemic vascular resistance, increases cardiac index, aggravates angina, and counteracts "vasopressor" (fibrinogenic) drugs [307,314,315,332,343,349-352]; why allostatic load inhibits insulin effects [353]; and why diabetes and hypertension are closely-related [225,231,232,268-271,273, 276-279,315-317,321-323,348,354-363].

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) [187,228,364,365]. Astrocytes proliferate when exposed to thrombin and release TPA to ensure brain perfusion [87,228]. Their anticoagulant effects necessitate abundant tissue factor, which explains the exaggerated morbidity of brain injury [107,140,210].

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* [366-374]. 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 [375-377]. Defective VIIIC (true hemophilia) paralyzes capillary gate regulation, causing exercise intolerance, but capillary gate structure and anaphylaxis susceptibility remain intact [378-380].

8. THE TURBULENCE MECHANISM

Red cell mass 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 [381-385].

In pipes, turbulence causes viscosity (flow resistance) to increase exponentially with velocity in "Newtonian" fluids such as water and oil (**Figure 2**) [386]. Mammalian blood, however, is a "non-Newtonian" fluid that exhibits exponential *declines* in viscosity with increasing velocity. This is because bi-concave 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 [292,387-393]. Mammalian arterial blood flow during systolic ejection might thus be compared to electrical "superconductivity". The resulting hemodynamic efficiency explains the mammalian heart accelerates blood from 0 to 125 cm/s in a tenth of a second (**Figure 3**) and why the hearts of both elephant and

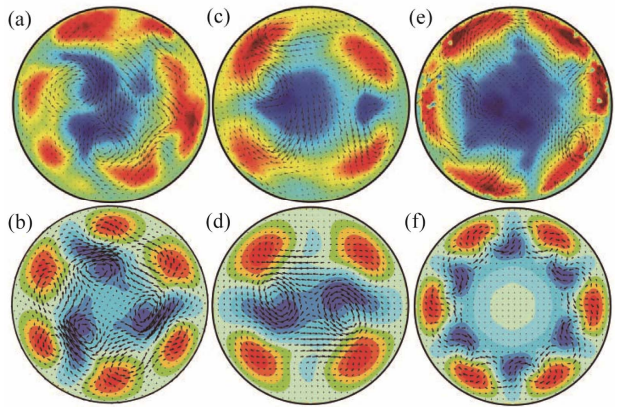


Figure 2. Newtonian pipe flow turbulence [386] turbulent forward flow appears as fast-moving "jet streams" (shown in red) that form along the inner walls of pipes and force slow-moving fluid to the center, where it moves *backward* (shown in blue), causing increased viscosity (flow resistance). (a), (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 re- sults shown by (a), (c) and (e). Similar arterial turbulence dur- ing 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.

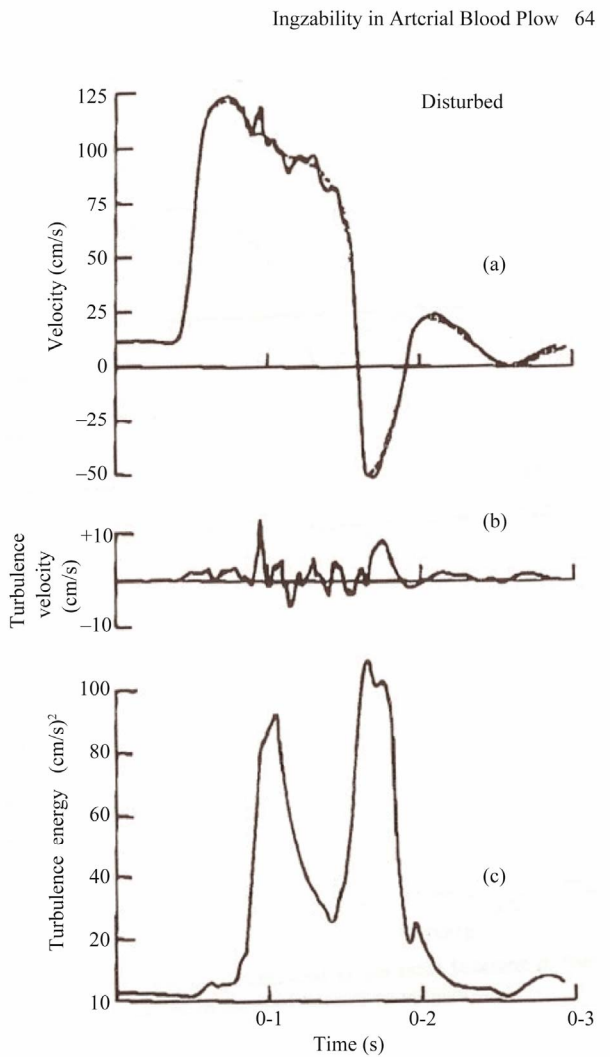


Figure 3. Turbulence and velocity in pulsatile blood flow in a dog. Mammalian red blood cells spontaneously form aggregates that suppress turbulence during systole to enable rapid and efficient blood acceleration. Diastolic deceleration disrupts the aggregates and converts laminar systolic flow into diastolic turbulence that halts net forward flow [395]. In humans, the brief flow reversal in the distal aorta inhibits turbulent cleansing and accelerates atherosclerosis relative to the proximal aorta [408].

mouse weigh only 0.6% of their body weight [394]. 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 [395,396].

Diastolic turbulence is inversely related to red cell mass. Polycythemia accelerates atherosclerosis and increases coagulability. Anemia progressively retards atherosclerosis and paralyses coagulation [176,397-403].

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 [236,405-407]. 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 [196,221,222,327,408-416].

The washing machine demonstrates how shear stress induces turbulence, and how viscosity exponentially inhibits turbulence even though it has no effect on shear stress. The rotor mechanism of the washing machine corresponds to the heart. The mixture of soap, water, and dirty clothes corresponds to blood. Like the heart, the rotor mechanism of the washing machine generates consistent work with each cycle. The force induced by the rotor corresponds to shear stress. Each times the rotor changes direction, it causes a burst of turbulent mixing that exponentially increases contact between soap, clothes, dirt, and water to enhance the ability of soap to clean clothes. The clothing load corresponds to blood viscosity. With reasonable clothing loads, turbulent mixing is optimized, and cleaning proceeds efficiently. If the

machine is overloaded, the rotor energy is shifted in favor of turbulent lateral forces at the expense of turbulent mixing, and the clothes are not cleaned properly. Similarly, increased blood viscosity alters diastolic pulsatile blood turbulence in favor of turbulent lateral forces that increase blood pressure at the expense of turbulent mixing forces that inhibit atherosclerosis.

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 [305,306,422-431].

Like ultrasound, diastolic turbulence inhibits coagulation [432]. Thrombosis is rare in arteries, where turbulence is intense, but thrombophlebitis is common in veins, where turbulence is sluggish [433]. 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 [161,268,304,392,434]. 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 [435-440]. 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 [118, 183,185,196,268,385,396,424,432,441-451]. Insoluble fibrin binds red cells into a clot after it reduces turbulent mixing below a threshold [161,432,452].

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 [453]. The blood pressure cuff measures diastolic turbulent lateral forces 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 similar among most mammalian species because red cells and body temperature are nearly identical, and cardiac power generation is proportional to body size [394].

Hemodynamic relationships usually appear linear because turbulent variables are maintained within narrow 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 [454,455].

Reptilian red cells enhance systolic turbulence at the expense of cardiac output to prevent atherosclerosis caused by lipoprotein solidification at cool temperatures that exaggerates blood viscosity [456,457]. This limits reptile cardiac output and constrains the ability of reptiles to deliver oxygen to peripheral tissues, so that they must rely on anaerobic metabolism to sustain vigorous activity [458]. This explains why reptiles have limited exercise capacity. 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 [456,457,459,460].

9. THE TISSUE REPAIR COMPONENT, INFLAMMATION, AND APOPTOSIS

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. Its activity explains all aspects of the inflammation syndrome, including rubor, calor, dolor, edema, and loss of function.

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 [83,108,159].

Trauma disrupts the fragile vascular endothelium and directly exposes tissue factor to blood enzymes [88, 210, 212]. Factor VII activation by tissue factor *initiates* the enzymatic interaction and determines its magnitude and location [208,209,212]. Factors IX and X *amplify* Factor VII thrombin production to moderate levels that energize tissue repair [27,121,215]. Factor VIII then *accelerates* thrombin production to high levels to generate insoluble fibrin for hemostasis [30,93,94,121,182,410,461]. Pulsatile blood flow thrusts platelets into damaged tissues [462], where thrombin chemotaxis attracts them and insoluble fibrin binds them into a short-lived “white clot” [94]. 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 10), 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 [84,161,169,432, 452]. 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 [463,464]. Factors VII, IX, and X penetrate the clot and interact with tissue factor to generate thrombin, which reduces clot permeability and constrains thrombin production [29,126,212,463-465]. Tissue repair then proceeds in predictable stages, energized by optimized thrombin levels [135]. Thrombin elevations in damaged tissues cause cells to release bradykinins, caspases, prostaglandins, chemokines, cytokines, and interleukins. These induce inflammation and enable cell-to-cell communications that coordinate cell repair activities and determine the stages of wound healing [1,466-469]. Inflammation loosens cell connections to facilitate the entry and movement of soluble fibrin and repair cells [47]. Thrombin-generated soluble fibrin moves from blood through inflammatory gaps in the vascular endothelium to enter damaged tissues, where it creates a structural matrix that facilitates repair cell activity [149]. Thrombin elevation in damaged tissues attracts fibroblasts, myoblasts, osteocytes, and immune cells via chemotaxis, and these cells move through inflamed tissues into damaged tissues, where they proliferate and produce collagen, muscle, bone, and immune activity to fill empty spaces, replace damaged tissues, inhibit infection, and remove debris and foreign substances [108,109,159]. Thrombin-energized angiogenesis perfuses proliferating repair tissues. Thrombin-energized increases in cell metabolism cause temperature elevation in healing tissues. [133] As the repair process nears completion, proliferation and spreading of the vascular endothelium restores the normal barrier between blood enzymes and tissue factor in 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 [34,38,470,471].

The tissue repair component automatically forms abscesses, furuncles, and fistulas. Fibroblasts produce collagen to form barriers that isolate bacteria and foreign materials, and inflammation weakens surrounding tissues to create passages that expel them from the body. Trauma, burns, toxic chemicals, sepsis, and radiation disrupt the vascular endothelium, activate the tissue repair component, and release inflammatory substances that sensitize nociceptors and activate the capillary gate component. The delay between tissue damage and nociceptor sensitization explains the delayed onset of pain caused by radiation [213].

10. ANESTHESIA, ANALGESIA, ALLOSTASIS, 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. There are no clinically available means to inhibit the tissue pathway.

11. THE SPINAL PATHWAY

The spinal pathway consists of peripheral nociceptors in the skin and internal organs that detect noxious stimuli and activate the SNS via peripheral nerves and spinal cord internuncial pathways. Nociceptors detect vibration, temperature, inflammation and tissue disruption, but are insensitive to radiation, sepsis, and many toxic chemicals [472]. Spinal pathway activity is called *nociception*. Descending cortical pathways inhibit nociception, so that their absence exaggerates nociception [473]. Analgesic agents inhibit nociception by disrupting spinal pathway activity. Cyclo-oxygenase (COX) inhibitors prevent inflammation that activates nociceptors. Opioids inhibit spinal cord nociception pathways. Lidocaine, marcaine, and other local analgesics block the function of peripheral nerves, spinal cord pathways, and autonomic nerve endings that conduct nociception signals. The following examples illustrate spinal pathway function:

1) *Spinal Pathway nociception resists anesthesia* in safe and practical doses [153,474-479]. This explains the release of stress hormones (VWF, cortisol, epinephrine, glucagon, etc.) during surgery despite dangerously deep levels of anesthesia. It also explains spinal cord "wind-up" syndrome that causes problematic muscle tension and unexpected muscular movements during surgery despite deep levels of anesthesia.

2) Spinal cord damage at or above the level of T5 causes autonomic dysreflexia. The cognitive pathway no longer responds to nociception, so that pain is eliminated, but spinal pathway nociception, freed from descending cortical inhibition, causes harmful SNS hyperactivity that is little affected by anesthesia [473,480].

3) Cortical inhibition remains intact in spinal cord damage below the level of T5, and it inhibits spinal cord nociception pathways and synergizes the effects of general anesthetic agents in a manner analogous to analgesia [481-483].

4) Analgesia prevents both nociception and pain and thereby reduces surgical morbidity and mortality more effectively than anesthesia, which prevents only pain, fear, and apprehension (see Cognitive Pathway below) [153,479,481,484-504].

5) Pediatric anesthetic methods such as the once popular "Liverpool technique" that rely on inhalation agent supplemented by muscle relaxants do not adequately control stress. Fetuses and newborn babies cannot understand language and perceive danger, but their nociception pathways are fully functional so that they require analgesia as well as anesthesia for surgical safety [234,505-510].

6) I hypothesize that cortical damage sometimes impairs descending inhibition of spinal cord activity, so that spinal cord nociception pathway activity is exaggerated in the manner of autonomic dysreflexia (see #2 above). I further hypothesize that general anesthesia without supplemental analgesia exaggerates nociception by inhibiting cortical activity that is essential for descending pathway inhibition.

7) Nociceptors are not directly sensitive to radiation and some toxic chemicals, but they are indirectly and belatedly activated by inflammation that is induced by these forms of stress. For example, sunburn is initially painless, but becomes painful the day after sun exposure due to the inflammatory effects of radiation damage.

12. THE COGNITIVE PATHWAY

The cognitive pathway consists of conscious awareness generated by corticofugal mechanisms that assesses environmental hazards via sensory input including sight, smell, sound, vibration, and nociception. It activates the SNS and the HPA axis via hypothalamic pathways that are independent of the spinal pathway [191,250,511-514]. The cognitive pathway also inhibits spinal pathway nociception via descending pathways from the brain to the spinal cord [473]. Conscious awareness interprets nociception as *pain* [515,516]. Inhalation anesthetics are hypnotic agents that obtund consciousness. Even moderate inhibition of conscious awareness by hypnotic agents can eliminate pain, but hypnotic agents have little effect on nociception. The benefits of hypnotic inhalation anesthetic agents such as ether, halothane, chloroform, Ethrane, Isoforane, Desflurane and Sevoflurane are equivalent to those of intravenous hypnotic agents such as benzodiazepines, barbiturates, Propofol, ketamine, Etomidate, Althesin, Viadril, and alcohol.

Emotional mechanisms modulate cognitive pathway activity. This explains *allostasis*, which is the subconscious alteration of behavior and physiology in accord with prior experience. Hyperthymestic Syndrome demonstrates that the brain automatically records permanent audiovisual memories of all waking moments throughout life, and that these normally suppressed memories activate emotions and SNS activity [517,518]. Sleep halts the recording process while the emotional mechanism engages in the process of dreaming, wherein it automatically compares and contrasts previously stored memories to identify threatening circumstances [266,511,512,519]. This enables the pre-emptive perception of danger, whereupon emotional mechanisms automatically generate anxiety, rage, fear and apprehension, and activate the SNS and the HPA axis to facilitate "fight or flight" [520, 521]. This activates capillary hemostasis, and, increases blood viscosity [522], which limits blood loss in the event of subsequent injury. It also concentrates blood flow in critical organs such as heart, lung, and brain, whose tissues resist capillary hemostasis. The HPA axis simultaneously releases epinephrine, glucagon, cortisol, and other stress hormones. These combined effects explain the tachycardia, hypertension, and hyperglycemia, other reactions associated with acute and chronic allostasis, and how these reactions are progressively altered by accumulating memories and their ongoing manipulation by emotional mechanisms [523].

The emotional mechanism plays an important survival role in animals, which often face life or death confrontations and lack the reasoning ability of humans. Idiopathic Insomnia demonstrates that sleep and dreaming are not essential in humans [230,522,524-526]. However, occult allostasis explains neurosis in humans. It also explains how emotions alter the perception of pain and danger, which suggests new treatments for chronic pain and neurosis [527].

The following examples illustrate cognitive pathway activity:

1) The cognitive pathway activates the SNS 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 SNS [230,524-526,528-531].

2) The cognitive pathway resists analgesia in clinically practical doses, because sight, smell, vibration, and sound perception remain intact. Spinal and epidural analgesia, analgesic block techniques, and high-dose opioid analgesia for cardiac surgery often require supplementation with hypnotic agents to prevent sharp increases in blood pressure, pulse rate and muscle activity caused by frightening sounds and sensations, even though nociception

and pain are absent [153,474-478,532,533].

3) Anesthesia increases surgical safety by abolishing consciousness, fear, apprehension, and pain, but it cannot prevent harmful spinal pathway nociception in clinically practical doses [250,266,522,528,534-542].

4) Acute allostatic load, such as occurs in uninjured earthquake victims, activates the cognitive pathway and causes acute and residual elevations of VWF, Factor VIII activity, blood viscosity, blood coagulability, myocardial infarction, stroke, heart rate and blood pressure in accord with the severity of fear. This explains how people are sometimes frightened to death [441].

5) Chronic emotional allostatic load, such as job difficulties, elevates VWF and Factor VIII activity, accelerates atherosclerosis, and shortens life span [191,230,514, 520,529-531,543,544].

6) Moderate alcohol consumption inhibits consciousness and mitigates emotional distress, which reduces SNS activity, thus explaining its ability to prevent heart disease and enhance longevity [532,545,546].

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 [210].

13. THE TISSUE PATHWAY

The tissue pathway consists of the vascular endothelium, tissue factor, and Factor VII. The vascular endothelium manufactures tissue factor, excretes it into extravascular tissues, and insulates it from flowing blood. Tissue damage disrupts the vascular endothelium and exposes tissue factor to Factor VII in flowing blood, which activates Factor VII and initiates tissue repair. The tissue pathway activates the tissue repair component in accord with the magnitude and location of injurious forces that disrupt the vascular endothelium, expose tissue factor to Factor VII in blood, and release tissue factor into blood circulation with systemic consequences.

Brain, lung, nerves, autonomic ganglia, cervix, blood vessel adventitia, epithelium, mucosa, glomeruli, and placenta are rich in tissue factor [139,144,210,213,301, 547,548]. This explains why these tissues are “targets” for positive feedback in stress-related conditions. For example, severe brain and burn injuries release tissue factor into systemic circulation and exaggerate morbidity and mortality. Lung tissue reacts violently to microbes, antigens, and chemicals, causing lethal overproduction of soluble fibrin that floods alveolar spaces and airway passages and disrupts gas exchange in asthma, pneumonia, influenza, and poison gas exposure. Brain, lung, kidney, nerves, skin, cervix, and peri-arterial tissues are more likely to develop malignancies or be the site of metastasis than other tissues. Placenta, brain, kidney and lung function are primary targets in eclampsia. Adult Respiratory Distress Syndrome (ARDS) is usually the first manifestation of Multi-Organ Failure Syndrome (MOFS) that primarily affects lung, brain, and kidney.

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 profuse soluble fibrin exudates that flood alveolar spaces, disrupt gas exchange, and promote collagen generation (fibrosis) [146,147,549].

2) Inhaled antigens imperceptibly deposit on airway passages and induce soluble fibrin generation on their inner walls. This has minor effect during inhalation, when airway diameters are increased, but inhibits airflow during exhalation, when airway diameters are reduced, causing asthma [47,141,149,213,281,550,551].

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. Thrombin energizes inflammatory changes that enable soluble fibrin to enter extravascular tissues, causing tissue edema and organ dysfunction [140,552].

4) Brain and burn injuries release large amounts of tissue factor into blood circulation, causing abnormal systemic Factor VII activation that overwhelms inhibitory mechanisms and induces SRM hyperactivity and positive feedback that exaggerates morbidity and mortality [213].

5) Radiation does not directly activate peripheral nociceptors, but it damages the vascular endothelium, causing thrombin generation and positive feedback that energizes the release of inflammatory substances that activate nociceptors, causing belated pain. For example, skin damage due to sun exposure is initially painless and invisible, but the gradual onset of inflammatory effects caused by radiation damage produces a delayed painful reaction.

6) Site-inactivated tissue factor neutralizes the tissue pathway and inhibits the effects of sepsis [553-555].

7) Amniotic fluid is rich in tissue factor. Amniotic fluid embolus suddenly introduces large amounts of tissue factor into circulation, which activates Factor VII and induces capillary gate component hyperactivity that triggers spontaneous systemic coagulation activity that depletes coagulation precursors such as fibrinogen and fibronectin, causing defective coagulation activity known as Disseminated Intravascular Coagulation (DIC) (see below) [184].

14. POSITIVE AND NEGATIVE 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 [454]. The semi-independent and synergistic *spinal* and *cognitive pathways* both activate the capillary gate component, in accord with combinations of sight, sound, smell, vibration, 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 [177,368]. The capillary gate component activates Factor VIII, accelerates thrombin production, and generates insoluble fibrin [82,140,141,556-558]. The activity of each component exaggerates that of the other in a "chaotic" manner [454], because both share the enzymatic interaction of Factors VII, VIII, IX and X [297]. The simultaneous, synergistic activation of both components induces "positive feedback" so that peak SRM activity occurs several hours after injury [129]. The constantly fluctuating activities of the three synergistic pathways enable the SRM to focus its powerful effects and generate an infinite variety of manifestations [281,284,502-504,536,559-563].

As stressors subside, "negative feedback" restores homeostasis via clot formation and tissue repair that progressively reduces thrombin production to maintenance levels. Likewise, parasympathetic activity, Stoichiometric ATIII, TFPI, TPA and protein C mobilization [141, 148,281,564-566] restores homeostasis by inhibiting Factor VII and Factor VIII activity and accelerating the spontaneous disintegration of insoluble fibrin [116,141, 281,519,550,567-572]. However, prolonged Factor VIII half-life and spinal cord "wind up" can cause residual capillary gate component hyperactivity to linger long after stressors subside [139,144,148,157,210,573-575].

15. THE INFLAMMATION SYNDROME AND THE SRM

SRM activity explains the nature of disease, disease symptoms, and the relationships of physiology, pathology and stress[4]. Radiation, surgery, trauma, chemicals, sepsis, obesity, allergic reactions, myopathy, peritonitis, atherosclerosis, rheumatoid diseases, diabetes, exercise, malignancy, and other forms of stress cause systemic SRM positive feedback and hyperactivity that elevates thrombin generation and produces local or systemic inflammatory changes that can be either visible or occult.

Inflammation is a medical syndrome that is classically described as a combination of dolor (pain), rubor (redness), calor (heat), tumor (edema), and Functio laesa (loss of function). The simultaneous appearance and resolution of these seemingly unrelated visible symptoms remains unexplained. SRM activity explains all aspects of inflammation. It is most easily understood in terms of tissue repair. Coagulation is the first event in tissue repair. It stems blood loss and then governs thrombin generation in damaged tissues. Thrombin energizes the cellular release of chemokines, cytokines, prostaglandins, and bradykinins. These increase capillary perfusion, which causes redness (rubor); sensitize nociceptors, which causes pain (dolor); loosen cell connections, which enables chemotaxis; and enable cell-to-cell communications that govern the orderly sequence of cell activities during the repair process. Thrombin converts fibrinogen to soluble fibrin, which escapes from blood through inflammatory gaps in the vascular endothelium and diffuses into inflamed and damaged tissues. This causes tissue swelling and edema (tumor). Repair cells multiply and differentiate to increase immune activity and generate granulation tissue that fills wound cavities and replaces damaged tissues. This intense metabolic activity generates heat and elevates tissue temperature (calor). Pain and swelling immobilizes inflamed joints and tissues, causing loss of function (Functio laesa). The integrity of the vascular endothelium is restored as tissue repair nears completion, and this causes thrombin generation and inflammation to subside to maintenance levels. Thrombin starvation then undermines clot integrity, shrinks granulation tissues and draws wound edges together via apoptosis, and resolves the tissue repair process.

16. INFLAMMATION AND ATHEROSCLEROSIS

The SRM explains why inflammation is involved in atheroma formation. Atherosclerosis is a complex phenomenon that is explained by a combination of inadequate blood turbulence that causes particulate deposits to accumulate on the inner surfaces of arteries, and SRM activity that generates inflammation and plaque formation in response to these deposits.

Inadequate blood turbulence explains why atherosclerosis begins on the greater curvatures of arteries, where shear stress and systolic velocity decline and diastolic turbulence decreases exponentially [405-407,417-421]. High flow rates are necessary to generate turbulence that prevents sludge deposits in oil pipelines [404]. Similarly, pulsatile arterial flow operates at the threshold of peak diastolic turbulence to prevent particulate deposits on the inner walls of arteries that are the initial cause of atheroma formation. The vascular endothelium adjusts arterial diameter via neuromuscular control to optimize turbulent cleansing [236,405-407].

Arterial deposits activate the tissue repair component

[415]. Tissue repair component activity then causes thrombus formation, inflammation, tissue factor accumulation, fibrosis, and cholesterol trapping that produces atherosclerotic plaque [196,221,222,327,408-416].

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 [305,306,422-431]. The natural decline in cardiac index with advancing age accelerates atherosclerosis and explains its prevalence in old age.

Shear stress and viscosity both affect turbulence, but viscosity has no effect on shear stress and vice-versa. This explains why shear stress cannot explain atherosclerosis resistance in Down's Syndrome [576,577], hemophilia, von Willebrand coagulopathy [578], and patients treated with anticoagulants.

17. INFLAMMATION, APOPTOSIS, AND MALIGNANCY

The SRM provides a cohesive explanation of inflammation, apoptosis, and malignancy. The simplest explanation of apoptosis is thrombin starvation of repair cells. This normally occurs during tissue repair resolution. The SRM continuously governs thrombin levels in all tissues to energize, and thereby regulate, tissue repair. SRM hyperactivity generates thrombin elevations that induce repair cell hyperactivity that causes inflammation, which loosens cell connections to enable cellular repair activeties. As tissue repair nears conclusion, declining SRM activity restores thrombin to maintenance levels, which causes thrombin-dependent repair cells to undergo apoptosis. This shrinks granulation tissues in wound cavities and enables wound closure.

Cellular thrombin receptor configurations become altered during both embryological development and tissue repair, and exaggerated repair cell mitosis and metabolism during normal tissue repair causes abnormal chromosome morphology, so that the microscopic appearance of normal repair cell hyperactivity cannot be distinguished from malignancy [204,579-592]. Malignancy is an abnormal manifestation of tissue repair activity that occurs when prolonged and exaggerated positive feedback causes SRM repair hyperactivity to become self-sustaining [204,210,593]. Malignant cells invade normal tissues, release tissue factor, activate nervous sensors, and cause a "vicious cycle" of positive feedback that sustains abnormal thrombin elevations that inhibit the apoptosis and resolution that normally occurs at the conclusion of the tissue repair process [29,82,216,217,594-597]. For example, uncontrolled osteomyelitis sometimes evolves into osteosarcoma. Malignancy induces systemic SRM hyperactivity that causes systemic inflammatory effects and increases blood viscosity and coagulability. This increases the risk of infarction and metastasis. Brain, nerve, retina, ovary, placenta, lung, artery, and cervix tissues are rich in tissue factor and therefore especially vulnerable to both primary malignancy and metastasis [210,552,556,557,598-600]. SRM activity thus explains the close association of malignancy with chronic disease, environmental stress, inflammation, elevated Factor VII and Factor VIII activity, increased blood viscosity and coagulability, accelerated atherosclerosis, and seemingly unrelated forms of malignancy [556-558,566,601-605].

The SRM indicates an effective strategy for cancer prevention and treatment. Combinations of analgesia that inhibits the spinal pathway, anesthesia that inhibits the cognitive pathway, and treatments that inhibit the tissue pathway can mitigate positive feedback reduce the risk of malignancy, and induce apoptosis to cure malignancy [505-507,606,607].

The currently prevailing belief that defective DNA causes cancer is unfounded, and treatments based on this concept are notoriously ineffective. "The Secret History of the War on Cancer" by Devra Davis explains how current cancer beliefs and treatments became entrenched [592]. Drs. Goodman and Gilman of pharmacology textbook fame demonstrated that toxic war gases reduce white blood cell counts in leukemia, which they assumed was beneficial. Then they tested their toxic treatment on a mouse with a solid tumor, whereupon the tumor shrank dramatically. Though subsequent experiments produced unimpressive results, they assumed that they had discovered an effective cancer treatment strategy. Soon thereafter, the discovery of DNA provided the seemingly reasonable rationale that DNA damage causes cancer, which implies that killing cancer cells cures cancer. Thus chemotherapy seeks to induce apoptosis (programmed cell death) in malignant cells [608], while surgery and radiation therapy seek to extirpate and destroy them. Unfortunately, these conventional cancer treatments are harmful and unreliable. Surgery, radiation, and toxic chemicals all increase SRM activity, which explains why conventional treatments are accompanied by increased risk of cancer and cardiovascular disease [552,556,557,598-600]. They are plagued by toxic side effects and physical disfiguration, bedeviled by the subsequent appearance of other, seemingly unrelated, forms of cancer, and they increase morbidity and mortality from atherosclerosis, infarction, and pulmonary embolus [582]. They sometimes succeed, but only because hyperactive repair cells are more vulnerable to radiation and toxic chemicals than quiescent cells, and spontaneous apoptosis sometimes occurs despite the treatments. Conventional cancer treatments are comparable to fighting fire with oil. This can

succeed, but only if enough oil is poured fast enough to smother the fire. Otherwise, the oil may accelerate the fire, and residual oil increases the risk of subsequent fires.

18. INFLAMMATION AND SURGICAL STRESS

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 [505-507,606,607]. This manifests as symptoms distant from the location and time of surgery that are known as the surgical stress syndrome [238,239,328,474,475,482,487,505,506,510,532,533,546, 561,609-628]. Analgesia controls nociception, and prevents SNS activation via spinal cord pathways. Anesthesia controls conscious awareness, and prevents SNS activation via hypothalamic pathways that are independent of spinal cord nociception pathways. Either anesthesia or analgesia can independently reduce positive feedback and surgical stress to the point that most patients survive surgery [13,132], but outcome is further enhanced if synergistic combinations of anesthesia and analgesia are maintained continuously throughout surgery [233,238, 243,328,465,533,610,621,629-648]. Such combinations beneficially prevent thrombin acceleration, inhibit thrombin-induced immune activity and inflammatory effects [601], and reduce blood viscosity and coagulability. This improves tissue perfusion and oxygenation, protects organ function, maintains cardiac output, reduces blood pressure, increases ejection fraction, slows heart rate via the Starling Mechanism, and reduces the risk of malignancy and heart disease in the distant aftermath of surgery [201,210,213,479,508,551,649]. Theoretically, the additional neutralization of tissue factor released into blood during surgery should abolish the surgical stress syndrome.

19. INFLAMMATION AND SEPSIS

The thrombin-energized complement cascade attacks bacteria that enter the bloodstream [19]. Bacterial products cause inflammatory gaps to form in the vascular endothelium that allow soluble fibrin to diffuse from the bloodstream into extravascular tissues and organs, which causes tissue edema and disrupts organ function [47,141, 144,218,281,550,551]. Gaps in the vascular endothelium also allow tissue factor to escape into flowing blood, which activates Factor VII, which then interacts with Factors VIII, IX, and X to generate insoluble fibrin, increase blood viscosity and coagulability, and induce positive feedback in the SRM [213,281]. SRM hyperactivity thus explains the devastating inflammatory effects of sepsis.

20. SYSTEMIC INFLAMMATORY SYNDROMES

Eclampsia, amniotic fluid embolism, Disseminated Intravascular Coagulation (DIC), Multi-Organ Failure Syndrome (MOFS), and Adult Respiratory Distress Syndrome (ARDS) are all closely related. Combinations of stressful forces and stressful stimuli cause these pathologies by inducing severe systemic SRM hyperactivity and positive feedback, causing systemic inflammatory effects that disrupt organ function [139,144,148,157,210, 573-575].

MSOF commonly occurs after severe trauma, which causes nociception, pain, and fear and releases tissue factor into blood circulation. Trauma is often complicated by sepsis, cold, and other stresses that exaggerate the risk and severity of SRM hyperactivity [145,155,156, 175,307,650-660]. ARDS is typically the first manifestation of MSOF, because lung tissue possesses more tissue factor than other organs and is therefore affected sooner [661]. Inflammatory effects in the lung cause excessive soluble fibrin production that interferes with gas exchange. Pulmonary exudates in ARDS are similar to those in pneumonia and influenza, except that bacterial and viral invasion of the lung triggers SRM hyperactivity via direct lung tissue effects [4].

21. ECLAMPSIA AND AMNIOTIC FLUID EMBOLUS

Eclampsia is analogous to MSOF, except that it occurs in pregnant women. Pregnancy is a stressful condition characterized by SRM hyperactivity that elevates blood levels of Factor VIII, generates insoluble fibrin, and increases blood viscosity and coagulability [156,175,194, 657,658,662,663]. This is partially offset by Hemodilution anemia during pregnancy that increases blood turbulence and inhibits atherosclerosis [7,8]. Additional stress due to diabetes, obesity, and sepsis (commonly caused by occult urinary tract infections during pregnancy) exaggerates SRM hyperactivity and increases the risk and severity of eclampsia [51,81,112,113,133,138,200, 285,552-555,587,596,664-673]. The tranquilizing effects of smoking mitigate the severity of eclampsia [21,81,130, 673,674].

Eclampsia increases the risk of DIC, especially in the presence of amniotic fluid embolus. The developing fetus sheds tissue factor into amniotic fluid throughout pregnancy, so that amniotic fluid contains increasing concentrations of tissue factor as the pregnancy progresses. If amniotic fluid enters systemic circulation, it drastically increases Factor VII activity [193,200,554,555]. Factor VII then interacts with Factors VIII, IX, and X, which cause blood viscosity and coagulability to suddenly rise

above a critical threshold where spontaneous systemic coagulation (DIC) begins [675-679].

22. DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

The conversion of fibrinogen to soluble and insoluble fibrin is a complex process that involves several enzymes and precursors. Disseminated Intravascular Coagulation (DIC) illustrates how this process can go awry in several ways. DIC is usually caused by the abnormal entry of tissue factor into systemic blood circulation due to surgery, trauma, sepsis, and amniotic fluid embolus. This activates Factor VII, overwhelms inhibitory mechanisms (Protein C, TFPI, and ATIII), and initiates excessive intravascular generation of thrombin, soluble fibrin, and insoluble fibrin. The risk and severity of DIC is exaggerated by sensory stresses that activate Factor VIII. Insoluble fibrin exaggerates blood viscosity, which reduces blood turbulence below a threshold, whereupon spontaneous systemic coagulation suddenly begins [193,552, 680,681]. This rapidly consumes and depletes coagulation enzymes and precursors and distorts the coagulation process. Thrombin converts fibrinogen to soluble fibrin, which depletes fibrinogen [194,682]. Exaggerated Factor VIII activity converts Factor X to Factor XIII to convert soluble fibrin to insoluble fibrin, but this depletes Factor VIII and Factor X [163,172,188,194]. Factor XIII installs "cross-links" of fibronectin and plasminogen to soluble fibrin to generate insoluble fibrin, and this consumes both Factor XIII and fibronectin [680,681]. Shortages of Factor XIII and fibronectin cause soluble fibrin to accumulate to excessive blood levels [169]. Fibronectin exhaustion also causes Factor XIII to produce defective forms of insoluble fibrin with inadequate fibronectin "cross-links" [160]. These imbalances cause soluble fibrin to form abnormal attachments to the pathological clots to produce "microthrombi". Soluble fibrin also deposits on arterial walls [197,198,683]. The abnormal coagulation activity reduces circulating red cell mass, which exaggerates blood turbulence and further inhibits effective coagulation. These abnormalities and imbalances cause the generalized failure of hemostasis that characterizes DIC [401,460,684].

DIC often occurs in patients who undergo extensive surgical intervention in the immediate aftermath of major trauma and massive blood loss [11,200,568]. Trauma and surgery both release tissue factor into systemic circulation and increase Factor VII activity, causing SRM hyperactivity and positive feedback [116,184,194,286,460, 542,660,684-686]. In addition, trauma patients are typically subjected to starvation, sepsis, hypothermia, fear, pain, hypoxia, and iatrogenic hyperoxia, and these additional forms of stress exaggerate positive feedback and SRM hyperactivity.

Misguided treatments can confuse and aggravate DIC. Crystalloids, colloids, and starch solutions briefly dilute coagulation precursors and enzymes, alter blood turbulence, and exaggerate blood pressure, which conveys the misleading impression that they improve cardiac output [384,687,688]. DIC removes red cells from circulation, causing anemia that exaggerates blood turbulence and inhibits coagulation [457]. Blood transfusion corrects the anemia, reduces blood turbulence, and restores blood coagulability, but excessive transfusion with washed, packed red cells can reduce blood turbulence below a critical threshold and aggravate the problem. Reduction of body temperature even slightly below normal mammalian body temperatures causes lipoprotein solidification, which harmfully increases blood viscosity [660]. Cold stress activates the SRM and increases blood levels of insoluble fibrin, which also increases blood viscosity [401]. Severe hypothermia impairs SRM enzymes, and inhibits hemostasis [459]. Metabolic acidosis and hypothermia synergistically impair hemostasis [657].

23. EMBRYOLOGY, APOPTOSIS, AND THE SRM

As expected by the previous generation of stress theorists and researchers, the SRM explains the mysteries of embryological development. Cell proliferation and differentiation occurs faster during embryological development than at any other time of life. Symmetrical and asymmetrical structural development occurs in three dimensions. Ancient structures and organ systems such as the notochord and primitive renal systems appear and then or coalesce via apoptosis. The DNA mechanism by itself cannot explain these phenomena, because it does not explain how genetic information controls cell proliferation, cell maintenance, cell differentiation, and apoptosis.

Most presently available DNA information derives from prokaryotes, because these are easy to study. Prokaryotic (bacterial) cells employ their outer membrane for respiration, which limits them to single-cell existence, small size, and a few shapes that optimize surface area. They have simple internal structures and only one type of DNA that floats freely in the cytoplasm and transmits its genetic information via a straightforward mechanism that employs RNA templates to generate proteins. Unfortunately, the eukaryotic cells in complex animal are considerably more complex than prokaryotic cells, so that prokaryote information is often irrelevant to animal biology. Eukaryotic cells are believed to have originated when a "parent" cell somehow engulfed other types of previously free-living single-cell organisms (mitochondria, Golgi apparatus, endoplasmic reticulum, etc.) that subsequently became symbiotic organelles. The DNA of the "parent" cell exists in the form of chromosomes that are enclosed within a nuclear membrane that isolates

them from the cytoplasm. The engulfed organisms persist in the form of cytoplasmic "organelles" including mitochondria, endoplasmic reticulum, Golgi apparatus, and vacuoles. These possess DNA that replicates and functions independent of chromosome DNA in the nucleus. Eukaryotic cells utilize the mitochondria for aerobic respiration, which enables them to become much larger than prokaryotes, assume diverse shapes, engage in locomotion, and build multicellular life forms [689].

Unlike the DNA of prokaryotes, the nuclear DNA of eukaryotic cells transmits its genetic information via mechanisms that are not yet understood. Eukaryotic nuclear DNA consists of short protein-encoding segments that are interspersed with large sections of "junk" DNA that remains inert in the mature individual. "Junk" DNA was originally assumed to lack function, but recent research reveals that it consists at least in part of "introns" that control embryological development. However, introns do not produce proteins in the manner of DNA in prokaryotic cells. Modern researchers therefore suspect that introns control embryological development via a cytoplasmic mechanism that is different from prokaryote DNA mechanisms [31,690-692].

The previous generation of researchers expected that Selye's mechanism would function as a "companion mechanism" that works closely with DNA to convert genetic information into embryological structures. They postulated that DNA becomes quiescent once embryological development is complete, while the "companion", mechanism remains active throughout life to maintain and repair mature structures.

Both viewpoints may be correct. Thrombin receptors are present on the outer surface of all animal cells thus far tested, and they determine how cells respond to thrombin elevations. Mature animal cells have stable thrombin receptor configurations that characterize cell types, but cells alter these configurations during tissue repair and malignancy, and they can presumably alter them during embryological development as well [25,81, 693]. Animal cells also possess precise timing mechanisms that are critical to embryological development [694]. The simplest explanation is that introns control embryological cell proliferation, differentiation, and apoptosis by releasing tissue factor and altering thrombin receptor configurations in specific locations at precise time intervals. Thrombin receptor configurations control cell function, and tissue factor activates the SRM to generate thrombin that energizes cell activity. Such a mechanism would explain how introns govern embryological development in three dimensions. For example, it would explain how both right and left thumb development proceeds simultaneously, even though there is no direct communication between the two sets of tissues. This mechanism would explain how embryological cell differentiation and proliferation occurs faster during embryological development than at any other time of life, why introns do not generate proteins, and why defects in Factors VII, X and tissue factor disrupt embryological development, while defects in Factors VIII, IX, and XIII do not.

24. CONCLUSIONS

There is growing frustration with the lack of theoretical progress in biological and medical science [695,696]. The DNA paradigm has dominated research since stress theory was abandoned. DNA has revolutionized genetics and criminal justice, but it has failed to explain either embryological development or adult biology. The Genome Project illustrates this failure. It cost billions of dollars and it promised to revolutionize medicine, but it failed to produce a single treatment [695]. Scientific history suggests that the DNA paradigm must soon be replaced or reinvigorated by a new paradigm that will re-inspire scientific research [697].

Meanwhile, Selye's theory has never been refuted, and its virility remains undiminished. The SRM corroborates stress theory, complements and extends DNA theory, and exceeds the previous predictions of stress researchers. Inflammation and apoptosis illustrate the power of stress theory. Apoptosis explains key aspects of tissue repair, embryology, and malignancy. Inflammation appears in diverse circumstances and causes disparate symptoms (pain, swelling, heat, redness, and loss of function) that can now be understood as manifestations of SRM hyperactivity. Inflammation plays an essential role in tissue repair, but it can be harmful or even lethal when excessive, so that control of SRM hyperactivity confers improved outcome.

The SRM explains far more than inflammation and apoptosis. It provides fresh insights to embryology, evolution, taxonomy, anatomy, behavior, intelligence, pharmacology, physiology, pathology, stress, and their relationships. It enables Selye's Universal Theory of Medicine, which promises to elevate medicine from an art based on experiment to a science founded on theory. Stress theory is thus poised to complement and rejuvenate the DNA paradigm, and inspire productive research and pharmaceutical development. It portends a new era of health, longevity, productivity, and freedom from the eternal scourge of disease.

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