30 Years Lost in Medical Theory: Hans Selye’s Unified Theory of Medicine and the Stress Repair Mechanism

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Abstract

In 1951, Hans Selye hypothesized that a single mechanism continuously repairs and maintains the vertebrate body. The discovery of this mechanism would enable a “Unified Theory of Medicine” by explaining the nature of physiology, pathology, stress, and their relationships. Such a theory would vastly enhance pharmaceutical development and medical treatment.

Soon after Selye published his theory, the discovery of DNA inspired great excitement in medicine and biology. Many believed that the secret of life was at hand. It was widely anticipated that the stress mechanism works closely with DNA to enable embryological development, because the DNA mechanism by itself does not explain this. DNA would then resume quiescence, but the stress mechanism would remain active to maintain and repair mature structures. These powerfully simple ideas inspired an intense international search for the stress mechanism that lasted 30 years and consumed hundreds of research careers, thousands of test animals, and millions of dollars.

Stress researchers proposed two important theories to facilitate their research. Capillary gate theory postulates a submicroscopic mechanism that governs capillary blood flow and provides a superior explanation of hemodynamic physiology. Tissue repair theory postulates a single mechanism that governs tissue repair. Unfortunately, the two theories seemed incompatible. The era of stress research produced numerous important scientific advances, but no clue could be found to the existence of testable mechanisms that could confirm either capillary gate theory or tissue repair theory, let alone a single mechanism that explains both.

Selye’s ideas were never refuted, but the search for a mechanism of tissue repair was mostly abandoned after 30 years of fruitless effort. Since then, the DNA paradigm has dominated biological research. DNA has revolutionized genetics and criminal justice, but it has failed to explain either embryological development or adult biology in complex life forms, and there is growing frustration with the lack of theoretical progress in the biological and medical sciences.1,2

Now, 60 years after Selye’s original prediction, fresh evidence from unrelated research has enabled the first crude description of the long-sought “Stress Repair Mechanism” (SRM) that maintains and repairs the vertebrate body. It closely resembles the “coagulation cascade” that appeared during the heyday of stress research, but fresh information enables the SRM to provide detailed explanations for hemodynamic physiology, hemostasis, and tissue repair, while the coagulation cascade provides only a crude description of clot formation. The SRM incorporates both the capillary gate and tissue repair theories in the form of semi-independent sub-components, each of whose activity exaggerates that of the other. This enables the SRM to focus its powerful effects to maintain and repair tissues, and explains how it generates a bewildering variety of dynamic effects. Its appearance explains the Cambrian Explosion, and it provides fresh insights to embryology and evolution. It enables Selye’s Unified Theory of Medicine that encompasses cohesive new theories of physiology, pharmacology, stress, tissue repair, anesthesia, analgesia, allostatics, atherosclerosis, amyloidosis, apoptosis, angiodyplasia, angiogenesis, anaphylaxis, capillary hemostasis, coagulation, edema, inflammation, fever, malignancy, metastasis, eclampsia, diabetes, hypertension, infarction, congestive heart failure, rheumatoid disease, Multi-Organ Failure Syndrome (MOFS), Adult Respiratory Distress Syndrome (ARDS), asthma, influenza, pneumonia, and sepsis. The SRM thus fulfills all the predictions and expectations of the previous generation of stress researchers. Stress theory is thus poised to complement and rejuvenate the DNA paradigm, and inspire a new era of productive research and pharmaceutical development.

Introduction

The ultimate objective of medical science is a theory that explains physiology, pathology, stress, and their relationships. Such a theory would vastly enhance the effectiveness and reliability of medical treatments, and enable efficient and profitable pharmaceutical development. Unfortunately, vertebrate
biology remains stubbornly mysterious and confusing. Vertebrates obviously possess the means to maintain and repair their body structure, but the means remains unknown. Despite the discovery of DNA, embryological development remains a mystery. The physiological differences among reptiles, amphibians, birds, and mammals remain obscure. The nature of blood pressure, the palpable pulse, atherosclerosis, cancer, eclampsia, apoptosis, amyloidosis, sepsis, eclampsia, rheumatoid diseases, hemoglobin encapsulation, and the regulation of blood flow and cardiac output remain obscure. Lacking such understanding, medicine remains an art based on experiment, where physicians must judge their treatments in terms of symptoms, so that they are often inefficient, unpredictable, or counterproductive.

In 1951, Hans Selye postulated the presence of a “stress mechanism” that continuously repairs and maintains vertebrate tissues. Selye’s theory provided the simplest explanation of physiology, pathology, stress, and their relationships, and it promised a revolutionary Unified Theory of Medicine. Only three years later, Watson and Crick discovered DNA. Their unprecedented achievement caused enormous excitement that is difficult to appreciate from our distant perspective. Many believed that the secret of life was at hand. It was widely expected that the stress mechanism works closely with DNA to convert genetic information into embryological development, and then remains active throughout life to maintain mature structures, while the DNA mechanism resumes quiescence once embryological development is complete.

Selye’s pioneering ideas established a science; introduced the concepts of stress, stressor, eustress, distress, fight or flight, and the general adaptation syndrome. They inspired an international search for the putative stress mechanism that lasted 30 years and consumed a generation of researchers, thousands of test animals, and millions of dollars. These efforts produced capillary gate theory, which postulates a sub-microscopic mechanism that regulates capillary flow, and tissue repair theory, which postulates a single mechanism that regulates the orderly sequence of tissue repair. The intense scientific research during this era clarified photosynthesis, identified the coagulation cascade and the Krebs cycle, and established the relationship of Hypothalamic-Pituitary-Adrenal (HPA) hormones and immune system activity to stress. It accumulated a solid body of evidence that stress induces HPA hormone release, elevates immune activity, and otherwise induces harmful effects in the vertebrate body that are inhibited by anesthesia and analgesia. More recently, the terms allostatic and allostatic load have supplanted Selye’s classical terms to acknowledge the ability of animals to adjust their behavior and maintain homeostasis in the presence of stress, but explanations of these phenomena have never been satisfactory for lack of an explanation of tissue repair.

The DNA paradigm has dominated medical science and research for the past 30 years since stress theory was abandoned. The DNA mechanism by itself does not explain how genetic information is converted into embryological development. In theory, continuous DNA/RNA signaling might explain adult biology, but despite more than 60 years of intense research, there is no convincing evidence that supports this idea. On the contrary, available evidence indicates that environmental factors are the most significant influence in adult biology, and this is difficult to explain purely in terms of DNA/RNA signaling. There is growing frustration with the lack of progress in biological research, most of which is inspired by the DNA/RNA paradigm, and attempts to rationalize adult biology in terms of DNA/RNA signaling are ever more strained and tenuous. This suggests that the utility of the DNA/RNA paradigm is reaching the limits of its utility as a scientific theory. Meanwhile, Selye’s idea was never disproved, and its theoretical potency remains undiminished, but the search for the stress mechanism was almost completely abandoned after no clue to its existence could be found. Since then, prominent experts have pronounced that no single mechanism could possibly explain the seemingly incompatible capillary gate and tissue repair theories, as well as the bewildering multitude of stress manifestations. However, this turns out not to be the case.

Powerful scientific theories often appear long before their time, and must await the death of critics and the accumulation of supporting evidence before they are embraced. That seems to be the fate of Selye’s ideas. 60 years after its origin and 30 years after its demise, fresh evidence has finally enabled
the first testable description of the long sought “Stress Repair Mechanism” (SRM) that explains stress theory. The SRM was identified after fresh information about coagulation Factor VIII inspired an extensive review of scientific literature that was enabled by the Internet. The distinctive physical and enzymatic properties of Factor VIII served as a “Rosetta Stone” that deciphered SRM characteristics and first yielded a fresh explanation for coagulation, soon followed by explanations of atherosclerosis, capillary gate theory, and tissue repair theory. Finally, all of these seemingly disparate mechanisms were comprehended as elements of a single cohesive mechanism, and it became possible to describe the SRM.

Perhaps it is unsurprising that the SRM has remained elusive, because it is complex, counterintuitive, and at odds with most prevailing medical beliefs, practices, and assumptions. Daunting evidence of the relationships between coagulation, tissue repair, and nervous activity has long existed, but missing pieces of the puzzle have made it impossible to explain until very recently. Without an effective explanation, medical science has treated coagulation as an independent process that is unrelated to nervous activity, hemodynamic physiology, and tissue repair, and whose sole purpose is to stem blood loss. Practitioners and researchers may therefore be startled to learn that coagulation enzymes are key elements of a cohesive mechanism that regulates tissue repair, hemodynamic physiology, and hemostasis in accord with combinations of nervous activity and tissue disruption.

The previous generation of stress researchers was closer to success than they could have known. As they suspected, the vascular endothelium and blood-borne “coagulation” enzymes are the focus of SRM activity. They would be gratified that their capillary gate and tissue repair theories paved the path to SRM discovery, but surprised that these seemingly incompatible concepts represent sub-components of a cohesive mechanism. They might also be startled to see that the coagulation cascade that appeared during the heyday of stress research is strikingly similar to the SRM. Its “intrinsic pathway” is analogous to the “tissue repair component” of the SRM. Its “extrinsic pathway” is analogous to the “capillary gate component” of the SRM. Its “final common pathway” is clarified and extended by the previously unappreciated roles of thrombin, soluble fibrin, and insoluble fibrin. The two SRM components operate independently, but they share the dynamic interaction of coagulation Factors VII, VIII, IX and X that generates thrombin, soluble fibrin, and insoluble fibrin, whose combined effects account for all SRM manifestations. The extravascular tissue repair component regulates Factor VII to generate thrombin and soluble fibrin for tissue repair. The intravascular capillary gate component regulates Factor VIII, which accelerates thrombin generation to convert soluble fibrin into insoluble fibrin to enable hemostasis and regulate tissue perfusion, organ function, and tissue repair. Because they share the same enzymes, the activity of each component exaggerates that of the other to induce positive feedback that produces rapid, powerful, and focused responses to stressors, and their independent fluctuations explain the bewildering multitude of SRM manifestations that belie the presence of a single mechanism. If stressors subside, the subsequent tissue repair process invokes negative feedback in the form of tissue repair that restores SRM activity to maintenance levels. However, prolonged and exaggerated stressor activity causes positive feedback to overwhelm negative feedback with pathological consequences. Therefore, control of the SRM confers the ability to improve outcome in numerous pathological conditions. The SRM thus enables Selye’s Unified Theory of Medicine. This essay will describe the SRM and discuss its operation and its implications in detail.
The Stress Repair Mechanism (SRM)

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.

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

**Stress Theory and the SRM**

SRM activity explains tissue repair and other manifestations of stress, homeostasis, allostatic, allostatic load and their relationships that cannot be explained by HPA hormones and immune activity alone. Without an effective explanation of tissue repair, the effects of stress have often been attributed to immune activity or stress hormones (epinephrine, norepinephrine, cortisol, glucagon, chemokines, cytokines, and so forth), both of which are routinely elevated in accord with SRM hyperactivity. For
example, diabetes and rheumatoid diseases are imputed to be “autoimmune” phenomena. These and other mysterious pathologies are better explained by dysfunctional SRM hyperactivity that elevates immune activity and releases chemokines, cytokines, and other substances that are normally generated by the SRM during tissue repair. Surgical stress illustrates these differences because it stimulates Sympathetic Nervous System (SNS) activity that increases both SRM activity and HPA hormone release. The HPA hormones typically normalize within 24 hours, and therefore cannot explain the distant manifestations of surgical stress. Meanwhile, SRM hyperactivity peaks around 48 hours and persists for months. SRM hyperactivity explains all known manifestations of the surgical stress syndrome, including increases in heart disease and malignancy in the distant aftermath of surgery (see “surgical stress syndrome” below)17, 21.

The SRM clarifies stress theory terms, as follows:

**Allostasis** is the process that enables an organism to maintain homeostasis in the presence of environmental stress through adaptation or change22, 23. 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 provides a fresh explanation. Emotional mechanisms continually adapt to environmental circumstances by altering autonomic balance to regulate hemodynamic physiology and facilitate “fight or flight” (see “allostasis” below)24, 25.

**Allostatic Load** is physiological “wear and tear” on the body that results from ongoing adaptive efforts to maintain stability (homeostasis) in response to environmental factors26-28. 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.

The SRM 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 capacity29, 30. Endurance conditioning causes the SRM to induce angiogenesis (capillary proliferation) that reduces vascular resistance, increases ejection fraction (which lowers resting heart rate), and increases exercise capacity31-37. **Distress** is synonymous with disease. Harmful SRM hyperactivity produces excessive or defective quantities of thrombin, soluble fibrin, and insoluble fibrin and exhausts their precursors including Factors VII, VIII, IX and X, tissue factor, von Willebrand Factor, ATP, fibrinogen, vitronectin, and fibronectin (see “DIC” below)38-46.

The SRM is consistent with the general adaption syndrome and extends it. **Alarm** is cognitive pathway activity (see “cognitive pathway” below) that detects and assesses danger, chooses between fight and flight, and activates the capillary gate component via hypothalamic pathways (see “capillary gate component” below). **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, Soluble Fibrin and Insoluble Fibrin**

**Thrombin** is the “universal enzyme of extracellular energy transduction.” Though it is conventionally regarded as a “coagulation enzyme,” it also energizes tissue repair. It transforms ATP energy into both cell and enzyme activities47-59. Thrombin affects all cell types thus far tested via their protease activated receptors (PAR), which vary in type and number according to individual cell types50, 58, 60-68. Thrombin activity requires Ca+, and parathyroid glands regulate extracellular Ca+ to optimize its activity29, 69-82. Mg+ competitively inhibits Ca+ and mitigates thrombin activity69, 78, 83-99. Thrombin increases intracellular Calcium levels and mitochondrial activity via PAR-1 receptors48, 58, 63, 72, 92, 100-103.
All cells thus far tested possess PAR (thrombin) receptors that are present in various combinations that are characteristic of specific cell types, and these determine cellular reactions to thrombin \(^{104, 105}\). PAR (thrombin) receptors can be over-expressed during both malignancy and normal wound healing \(^{52, 106}\).

The SRM continuously generates thrombin in all tissues to energize tissue maintenance \(^{107, 108}\). It accelerates thrombin generation to energize hemostasis immediately after injury \(^{109}\). It then maintains lesser thrombin elevations to energize tissue repair \(^{104}\). As healing nears completion, it reduces thrombin to maintenance levels, causing clot disintegration and apoptosis of repair cells that facilitates wound closure \(^{30, 64}\). 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 \(^{29, 104, 105, 110}\)
- Mitosis \(^{29, 68, 107, 111, 112}\)
- Metabolism \(^{29}\)
- Hypertrophy \(^{29, 105, 113-116}\)
- Angiogenesis \(^{48, 102, 117}\)
- Platelet activation, chemotaxis, and thromboxane release \(^{47, 118-121}\)
- Proliferation, spreading and gap formation in the vascular endothelium \(^{103, 122}\)
- Release of chemokines, cytokines, interleukins, bradykinins, caspases, and prostaglandins \(^{61, 110, 115, 123-131}\)
- Production of bone, muscle, collagen and immune activity by osteocytes, myocytes, fibroblasts, and immune cells \(^{30, 55, 71, 100, 105, 111, 114, 116, 122, 132-134, 135, 136-142}\)
- Conversion of fibrinogen to soluble fibrin \(^{76}\) that facilitates tissue repair
- Conversion of fibrillar soluble fibrin to three-dimensional insoluble fibrin \(^{75, 109, 143-151}\) that enables hemostasis and regulates tissue repair and hemodynamic physiology
- Inflammation, which dissolves the “basement membrane” that binds cells in tight formation with one another and with the Vascular Endothelium to facilitate chemotaxis \(^{63, 71}\).
- Proliferation of astrocytes and glial cells in brain tissue \(^{68, 112}\)
- Activation of gelsolin that neutralizes Actin \(^{152}\)
- Complement activation that attacks foreign antigens \(^{153}\)
- T-cell activation independent of an immune response \(^{65, 134}\)
- Blast transformation in lymphocytes
- Increased macrophage phagocytic activity \(^{65, 72, 102, 117, 134, 139, 154}\)
- Activation of plasma (immune) cells and neutrophils \(^{139, 150, 155}\)
- Release of “Tumor Necrosis Factor” from microglial cells \(^{156}\)
- Tumor growth, malignancy, and fibrosis \(^{30, 56, 60, 64, 132, 133, 138, 157, 158}\)
- Inhibits apoptosis \(^{58, 60, 66, 67, 159, 160}\)
- Intracellular gap formation in the vascular endothelium that increases permeability \(^{103}\)
- Defects in Factors VII, X and Tissue Factor that disrupt thrombin generation necessary for embryological development and tissue repair are generally lethal \(^{161}\)
- Embryological development, tissue maintenance, wound healing \(^{51, 101, 107, 108, 162}\)

Older studies have confused fibrinogen, soluble fibrin, and insoluble fibrin, because they are nearly identical chemically \(^{151, 163-166}\). 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 defective forms of insoluble fibrin are produced when fibrinogen is depleted \(^{143, 167}\). It consists of alpha, beta and gamma subunits that are connected by disulfide bonds \(^{151}\). Thrombin disrupts
the disulfide bonds and enables the alpha, beta, and gamma fibrinogen subunits to polymerize into fibrillar (two-dimensional) strands of "soluble fibrin"176, 103, 149.

**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 deposits168, 169. 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 55, 76, 103, 111, 148, 159, 168. 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 asthma163, 168, 170, 171. Soluble fibrin deposits promote collagen production, fibrosis, sclerosis, adhesions, and scar formation142, 164, 165, 172-183. 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 production133, but most anticoagulants have minimal effect on soluble fibrin deposits and collagen scars once they have formed184.

**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 repair146, 149, 185, 193. 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" drugs194.

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 XIII187, 191, 192. 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 together46, 193, 195. 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)148, 196-199. Parasympathetic Nervous System (PNS) activity stimulates the release of nitric oxide, which binds avidly to Ca++, inactivates thrombin, and accelerates the disintegration of insoluble fibrin69. 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 adhesions200, 201. Like normal patients, they produce excessive quantities of soluble fibrin in accord with pneumonia, influenza, ARDS, MOFS, asthma, and eclampsia170, 171, 179-181, 202. 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)118, 193, 196, 203-209. 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 hemostasis210, 212. 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 severe213-215.
Insoluble fibrin elevations cause increased viscosity and coagulability that pre-disposes to Disseminated Intravascular Coagulation (DIC), thrombophlebitis, pulmonary embolus, and accelerated atherosclerosis. 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, mental disturbances, myocardial infarction, renal dysfunction, bowel infarction, bowel ileus, and increased vascular resistance.

The Central Role of the Vascular Endothelium

The vascular endothelium is the focus of SRM activity. It 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 activates the tissue repair component (see “tissue repair component” below). Endothelial cells respond to their immediate surroundings and communicate with one another via electrical signals. Endothelial cells also produce fibronectin, vitronectin, tissue factor pathway inhibitor (TFPI), protein C, and tissue plasminogen activator (TPA) to enable and regulate SRM function.

The Dynamic Interaction of Factors VII, VIII, IX, and X

The interaction of hepatic enzyme Factors VII, VIII, IX, and X generates thrombin, soluble fibrin, and insoluble fibrin. Tissue factor activates Factor VII to initiate the interaction, Factor VII slowly and continuously penetrates the intact vascular endothelium and enters extravascular tissues, where tissue factor activates it. This continuously generates small amounts of thrombin in all tissues to energize tissue maintenance, but thrombin generated by Factor VII alone is insufficient for hemostasis or tissue repair. Tissue injury disrupts the vascular endothelium and exposes tissue factor to Factors VII, VIII, IX and X simultaneously. The resulting interaction accelerates thrombin generation to energize platelet activation and clot formation. The viscoelastic clot then substitutes for the damaged vascular endothelium and regulates contact between blood enzymes and tissue factor in injured tissues. Factor VIII cannot penetrate the clot due to its large physical size. Factors VII, IX, and X penetrate the clot to interact with tissue factor and generate thrombin in levels that energize tissue repair (see “Tissue Repair Component” below).

The priority of tissue development, maintenance, and repair is illustrated by anticoagulants and defects that affect Factors VII, X and tissue factor and disrupt embryological development, tissue maintenance, and tissue repair. In contrast, defects in hemostasis Factors VIII, IX and XIII are non-teratogenic and survivable. Heparin is non-teratogenic because it affects only Factor VIII.

The SRM Components

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. Factors IX and X are produced continuously, so they do not fluctuate. 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. Trauma disrupts the fragile vascular endothelium and directly exposes tissue factor to blood enzymes. Factor VII activation by tissue factor initiates the enzymatic interaction and determines its magnitude and location. Factors IX and X amplify thrombin production to moderate levels that energize tissue repair.

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Pulsatile blood flow thrusts platelets into damaged tissues, where thrombin chemotaxis attracts them and insoluble fibrin binds them into a short-lived “white clot.” 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” below), 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.

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. Factors VII, IX, and X penetrate the clot and interact with tissue factor to generate thrombin, which enhances insoluble fibrin generation and preservation, reduces clot permeability, and constrains thrombin production in the manner of negative feedback. This maintains thrombin at levels optimal for tissue repair. Tissue repair then proceeds in predictable stages. 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. Inflammation loosens cell connections to facilitate the entry and movement of soluble fibrin and repair cells. Soluble fibrin creates a structural matrix that facilitates the formation of granulation tissue that fills empty wound spaces. 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. Angiogenesis perfuses proliferating repair tissues. Increases in cell metabolism cause temperature elevation in healing tissues. As tissue repair 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.

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; and release inflammatory substances that activate the capillary gate component by stimulating its nervous sensors.
The Capillary Gate Component

The \textit{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 \textit{capillary gate mechanism} (see below) that regulates tissue perfusion, capillary hemostasis, and organ function, and a \textit{turbulence mechanism} (see below) that regulates blood viscosity (flow resistance), blood coagulability, and atherosclerosis \cite{274, 275, 309, 315, 318, 319, 321, 358}. 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 \cite{237, 238, 274-276}. Its \textit{acute} hyperactivation causes infarction, pulmonary embolus, thrombophlebitis, and high altitude pulmonary edema (HAPE)\cite{44, 216, 217, 222, 226, 290-308}. Its \textit{chronic} hyperactivation accelerates atherosclerosis and capillary senescence, and causes diabetes, hypertension, and organ failure \cite{241, 274, 275, 300, 309-321}.

The \textit{chimeric 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 (VWF) produced by the vascular endothelium and Factor VIIIC produced by the liver. These bind together to form Factor VIII in blood circulation and exert their effects in concert. Factor VIIIC is a hepatic enzyme that is released into blood at constant rates, but it is so labile that it cannot exert its enzymatic effects unless it is continuously stabilized by VWF. SNS activity releases VWF into blood, so that VWF blood levels constantly fluctuate in accord with stressful stimuli. SNS activity thus regulates the activity and half-life of Factor VIII. Factor VIII interacts with Factors VII, IX, and X to accelerate thrombin generation to energize its conversion of Factor X to Factor XIII. Factor XIII installs “cross-links” of fibronectin and plasminogen to convert soluble fibrin to insoluble fibrin in capillaries and flowing blood to “close” the capillary gate \cite{240, 322-328}. Continued Factor VIII activity inhibits the spontaneous disintegration of insoluble fibrin into inert fibrin split products via thrombin activated fibrinolysis inhibitor (TAFI)\cite{144, 193, 196, 206, 277}.

Parasympathetic nervous system activity disintegrates insoluble fibrin by releasing nitric oxide from the vascular endothelium to “open” the capillary gate. Nitric oxide is a ubiquitous gaseous signaling molecule that binds avidly to Ca$^{2+}$, which inactivates thrombin, and thereby accelerates the spontaneous disintegration of insoluble fibrin \cite{342, 289, 329-339}. Nitric oxide is also bactericidal, so that PNS activity inhibits infection as well as promotes tissue perfusion and oxygenation \cite{340}.

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 \cite{147, 199, 228, 230, 235, 243, 248, 254, 341-345}.

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 \cite{31-37, 51, 312, 346-354}. Allostatic load accelerates capillary senescence \cite{355-357}, which increases vascular resistance, impairs tissue and organ perfusion, inhibits glucose uptake, and causes diabetes and essential hypertension \cite{166, 219, 274, 275, 309, 315, 318, 319, 321, 358-364}.

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 \cite{238, 297, 330, 331, 365, 366}. 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

SNS activity “closes” the capillary gate by causing the vascular endothelium cells of the capillary walls to release von Willebrand Factor. 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. PNS activity “opens” the capillary gate by releasing nitric oxide from the vascular endothelium in viscera organs, including eye, brain, lung, GI tract, urinary tract, and pancreas via direct parasympathetic innervation. PNS activity also releases insulin, which releases nitric oxide from the capillaries of skeletal muscle and other peripheral tissues where direct PNS innervation is absent. This explains why insulin prolongs bleeding time, reduces systemic vascular resistance, increases cardiac index, aggravates angina, and counteracts “vasopressor” (fibrinogenic) drugs; why allostatic load inhibits insulin effects; and why diabetes and hypertension are closely related.

Nitric oxide is also bactericidal, so that PNS activity inhibits infection as well as enhances tissue perfusion and oxygenation.

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)

Angiodysplasia, Angioneurotic Edema, Coagulopathy, and the Capillary Gate Mechanism

Coagulopathies reveal capillary gate characteristics. Capillary structural integrity requires VWF, so that chronic VWF damage and/or deficiency cause flow-related capillary damage called angiodysplasia as well as von Willebrand coagulopathy. Sudden VWF destruction by complement (usually triggered by bee sting and other antigens) disrupts capillary gate structure, causing angioneurotic edema (anaphylaxis) 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. VWF is released from the vascular endothelium in accord with SNS activity, and this explains the fluctuating severity of the coagulopathy in individual patients. Defective VIIIC (true hemophilia) paralyzes capillary gate regulation, causing exercise intolerance, but capillary gate structure is not affected and patients remain susceptible to anaphylaxis.

A sex-linked gene controls VIIIC production. Defects in this gene that affect the quality or quantity of VIIIC production cause true hemophilia, which is transmitted by female “carriers” and primarily afflicts their male offspring. This infamous genetic defect plagued the royal families of Europe in the previous century. The condition causes a severe bleeding diathesis in most victims, but the severity varies in individual cases, depending on the ability of the individual patient to generate functional insoluble fibrin. This is reflected by 20-fold individual differences in blood viscosity and variable individual response to Factor VII therapy in hemophilia patients.

A somatic gene controls the production of von Willebrand’s Factor. Defects in the quality or quantity of its production cause von Willebrand’s Disease, which affects males and females equally. Its severe forms cause a bleeding diathesis that cannot be clinically distinguished from true hemophilia. Von Willebrand Disease is more common and usually much less severe than true hemophilia. Fluctuating levels of SNS activity that affect VWF levels and therefore affect Factor VIII activity and half-life explain
the fluctuating severity of the bleeding disorder observed in individual von Willebrand’s Disease patients 407, 420.

The Turbulence Mechanism

Hemoglobin encapsulation does not enhance oxygen delivery. Instead, red cell morphology alters blood turbulence, and thereby beneficially alters blood viscosity, coagulability, atherosclerosis, and hemodynamic efficiency 417, 418, 421-423. This explains why red cells are present in far greater quantities than needed for effective oxygen delivery.

In “Newtonian” fluids such as water and oil, pipe flow turbulence causes viscosity (flow resistance) to increase exponentially with velocity 424. 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 patterns that suppress systolic turbulence to optimize blood acceleration, cardiac output, and peak end-systolic velocity 335, 425-431. The resulting hemodynamic efficiency explains why the hearts of both elephant and mouse weigh only 0.6% of their body weight 432. 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 433, 434.

Diastolic turbulence is inversely related to red cell mass. Polycythemia decreases turbulence, increases coagulability, and accelerates atherosclerosis. Anemia progressively increases turbulence, paralyses coagulation, and retards atherosclerosis 203, 435-441.

Oil must flow through a pipeline at high rates to generate enough turbulence to prevent corrosive sludge deposits 442. Similarly, pulsatile arterial flow operates at the threshold of peak diastolic turbulence to prevent atherosclerosis. The vascular endothelium adjusts arterial diameter via neuromuscular control of vascular smooth muscle to optimize diastolic turbulent mixing, which mobilizes particulate deposits from arterial walls 279, 443-445. Without adequate turbulence, deposits form on the inner walls of arteries. This activates the tissue repair component, causing thrombin and soluble fibrin generation, inflammation, tissue factor accumulation, fibrosis, and cholesterol trapping that forms atherosclerotic plaque 223, 236, 237, 258, 364, 446-453.

Increased blood viscosity enhances turbulent lateral forces at the expense of turbulent mixing effects, and vice-versa. This explains how stress increases blood pressure and accelerates atherosclerosis, while stress control reduces blood pressure and retards atherosclerosis. The washing machine provides a convenient analogy. The rotor mechanism of the washing machine corresponds to the heart. The clothing load corresponds to blood viscosity. With reasonable clothing loads, the rotor mechanism induces turbulent mixing that increases contact between soap and dirt, 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.

Atherosclerosis begins on the greater curvatures of arteries, where shear stress and systolic velocity decline and turbulence decreases exponentially 443-445, 454-458. 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 5, 346, 347, 459-467.

Like ultrasound, diastolic turbulence inhibits coagulation 260. Thrombosis is rare in arteries, where turbulence is intense, but thrombophlebitis is common in veins, where turbulence is sluggish 468. 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. 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. 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. Insoluble fibrin binds red cells into a clot after it reduces turbulent mixing below a threshold.

Blood turbulence normally occurs below the threshold of hearing. Blood pressure cuff inflation constricts arterial diameter, increases flow velocity, alters the turbulent pulse wave and elevates turbulent frequencies above audible levels at the distal edge of the cuff to produce Korotkoff sounds that are analogous to bruit sounds. 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 viscosity that fluctuates in accord with autonomic balance is the main variable that affects blood pressure. Stressful stimuli activate the SNS, which causes the release of VWF from the vascular endothelium into flowing blood. This generates insoluble fibrin that elevates blood viscosity, reduces stroke volume, elevates heart rate via the Starling Mechanism, decreases cardiac output and tissue...
perfusion, increases blood pressure, and accelerates atherosclerosis. Stress reduction and parasympathetic activity decreases blood viscosity, increases stroke volume, retards atherosclerosis, reduces heart rate and blood pressure, and enhances tissue perfusion and organ function. Sleep is a state of minimal stress that is characterized by hypotension, bradycardia, enhanced tissue perfusion, and increased cardiac efficiency.

Hemodynamic relationships usually appear linear because turbulent variables are maintained within narrow ranges by mammalian physiology. Blood pressure is strikingly similar among most mammalian species because cardiac power generation is proportional to body size. However, turbulent relationships are exponential in nature, so that small changes can produce large differences. Multiple factors affect blood turbulence, including cardiac inotropy and chronotropy; arterial diameter and length; body temperature and lipoprotein solidification; red cell mass and morphology; and blood viscosity. 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.

Reptilian red cells enhance systolic turbulence at the expense of exercise tolerance to prevent atherosclerosis caused by lipoprotein solidification at low temperatures that sharply increases blood viscosity. Reptiles thrive in warm environments, but 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 lipoprotein liquefaction, which enables their bi-concave red cells to simultaneously optimize hemodynamic efficiency and atherosclerosis resistance, but this necessitates substantially greater caloric intake.

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. In humans, the brief flow reversal in the distal aorta inhibits turbulent cleansing and accelerates atherosclerosis relative to the proximal aorta.
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. There are no clinically 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 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. Spinal pathway activity is called nociception. Descending cortical pathways inhibit nociception, so that their absence exaggerates nociception. 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. 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 “windup” 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.

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.

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).

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.

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.

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 \(^{218, 293, 531-534}\). The cognitive pathway also inhibits spinal pathway nociception via descending pathways from the brain to the spinal cord \(^{494}\). Conscious awareness interprets nociception as pain \(^{535, 536}\). 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 \(^{537, 538}\). 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 \(^{308, 531, 532, 539}\). 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”\(^ {540, 541}\). This activates capillary hemostasis, and, increases blood viscosity \(^{542}\), 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 \(^{543}\).

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 \(^ {273, 542, 544-546}\). 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 \(^ {547}\).

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 \(^ {273, 544-546, 548-551}\).

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 \(^ {177, 495-499, 552, 553}\).
3. Anesthesia increases surgical safety by abolishing consciousness, fear, apprehension, and pain, but it cannot prevent harmful spinal pathway nociception in clinically practical doses. 

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. 

5. Chronic emotional allostatic load, such as job difficulties, elevates VWF and Factor VIII activity, accelerates atherosclerosis, and shortens life span. 

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. 

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. 

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, adventitia of blood vessels, epithelium of skin, mucosa, glomeruli, and placenta are rich in tissue factor. 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, 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). 

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. 

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 164, 571.

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 252.

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 572-574.

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) 211.

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 420. 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 204, 404. The capillary gate component activates Factor VIII, accelerates thrombin production, and generates insoluble fibrin 17, 18, 107, 164, 165, 575. The activity of each component exaggerates that of the other in a “chaotic” manner 420, because both share the enzymatic interaction of Factors VII, VIII, IX and X 341. The simultaneous, synergistic activation of both components induces “positive feedback” so that peak SRM activity occurs several hours after injury 189. The constantly fluctuating activities of the three synergistic pathways enable the SRM to focus its powerful effects and generate an infinite variety of manifestations 323, 526, 522-524, 556, 576-580.

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 restores homeostasis by inhibiting Factor VII and Factor VIII activity and accelerating the spontaneous disintegration of insoluble fibrin 142, 165, 323, 539, 569, 584-589. However, prolonged Factor VIII half-life and spinal cord “wind up” can cause residual capillary gate component hyperactivity to linger long after stressors subside 163, 168, 172, 181, 234, 590-592.

Eclampsia, ARDS, MSOF and DIC

Positive feedback that induces SRM hyperactivity explains the similarities of Multi-System Organ Failure (MSOF), Adult Respiratory Distress Syndrome (ARDS), eclampsia, malignancy, DIC, and
the surgical stress syndrome. Placenta, lung, cervix, brain, and peri-arterial tissues are especially vulnerable to SRM hyperactivity because they possess abundant tissue factor. MSOF commonly occurs after extensive injuries or sepsis, especially when both are present. ARDS is typically the first manifestation of MSOF, because lung tissue possesses abundant tissue and is therefore affected sooner than other organs. Eclampsia is a form of MSOF that is unique to pregnancy, which is a stressful condition. Additional forms of stress are invariably present in eclampsia, such as obesity, diabetes, rheumatoid disease, and urinary tract infection. Smoking mitigates the severity of eclampsia by tranquilizing cognitive pathway activity. SRM hyperactivity induced by eclampsia pre-disposes to DIC, especially in the event of amniotic fluid embolus that introduces tissue factor into blood circulation (see “DIC” below) MgSO4 therapy mitigates the symptoms of eclampsia by competing with Ca+ and inhibiting thrombin activity (see “Pharmacology and the SRM” below).

Malignancy

Devra Davis discusses the origin of the currently prevailing belief that defective DNA is the cause of cancer in her book “The Secret History of the War on Cancer”. Drs. Goodman and Gilman of pharmacology textbook fame conducted government-funded war gas research during WWII, shortly before Watson and Crick discovered DNA. They demonstrated that toxic war gases reduce white blood cell counts in leukemia, which they believed was beneficial. They subsequently tested their gas treatment on a mouse with a solid tumor, whereupon the tumor shrank dramatically. Though subsequent experiments produced far less impressive results, they believed that they had discovered an effective means to treat cancer. The coincidental discovery of DNA around this same time synergized with the toxic gas research and led to the seemingly reasonable assumption that defective DNA causes cancer, and that cells thus infested must be killed to effect a cure. This belief provides the basis for currently prevailing forms of cancer treatment, including surgical tumor excision, chemotherapy, and radiation therapy. The limited success of these treatments can be explained by the fact that malignant cells are more vulnerable to these destructive treatments than normal cells. However, the belief that defective DNA is the cause of cancer remains scientifically unfounded. Most evidence is at odds with this idea and indicates that cancer is caused by environmental stress, including the cancer treatments themselves. This explains why the incidence of cancer is rising in recent years despite these “modern” forms of treatment, and why conventional cancer treatments that produce “cures” are often bedeviled by the subsequent appearance of other, seemingly unrelated, forms of cancer, not to mention increased morbidity and mortality from heart disease, stroke, and pulmonary embolus.

Stress theory provides an improved explanation of cancer. Malignancy is aberrant repair-cell hyperactivity caused by positive feedback that induces persistent abnormal thrombin elevations. It may involve re-activated embryological thrombin receptor configurations (see embryology and evolution below). 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 that normally occurs at the conclusion of the tissue repair process. Brain, nerve, ovary, placenta, lung, artery, and cervix tissues that are rich in tissue factor are especially vulnerable to both malignancy and metastasis. 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. Combinations of analgesia that inhibits the spinal pathway, anesthesia that inhibits the cognitive pathway, and anticoagulants that inhibit the tissue pathway can mitigate positive feedback reduce the risk of malignancy, as well as improve the outcome of chemotherapy regimens.
**Anesthesia, Analgesia, and the Surgical Stress Syndrome**

The SRM provides a long-sought theory of anesthesia, analgesia, and allostatics that enables the alteration of anesthesia technique to optimize surgical outcome. Invasive surgery was avoided until anesthesia provided a practical means to ablate consciousness. This reduced stress, improved survival, and revolutionized surgery. However, anesthesia alone cannot prevent the “Surgical Stress Syndrome,” which consists of pathological symptoms that appear distant from the time and location of surgery. Even deep levels of anesthesia must be supplemented with muscle relaxants to prevent unexpected movements and troublesome muscle tension. An effective theory must explain these problems.

Attempts to establish anesthesia theory began with Meyer and Overton around 1896, but their lipid solubility theory proved invalid, and no subsequent effort has succeeded. The challenge became more daunting after 1914, when George Washington Crile demonstrated that adding analgesia to anesthesia improves surgical safety. This means that an effective theory must explain the confusing and overlapping effects of both anesthesia and analgesia. However, most efforts have focused on anesthesia and neglected analgesia. The need for an effective theory has recently become more urgent after clinical research produced unexpected evidence that anesthesia technique affects cancer and heart disease in the distant aftermath of surgery.

**Impediments to Anesthesia Theory**

Pre-existing beliefs, entrenched habits, and defective standards have obstructed anesthesia research, patient safety, and theory development. Most of these originated during the “Golden Era of Ether” that lasted from approximately 1860 to 1960, when anesthesia practitioners routinely observed that ether progressively reduces blood pressure and abolishes pain before it obtunds conscious awareness. This conveyed the conviction that anesthesia has dose-related analgesic properties that prevent Sympathetic Nervous System (SNS) stimulation by surgical stress. This lingering assumption has caused most theorists to neglect nociception pathways that bypass the brain and remain active despite anesthesia.

Also problematic is the counterintuitive mystery of hemodynamic physiology. The nature of blood pressure and the palpable pulse has never been understood. They became basic monitoring standards for lack of alternatives. Decreased cardiac output and tissue perfusion usually accompanies tachycardia and hypertension, while bradycardia and hypotension characterize enhanced cardiac efficiency and tissue perfusion, as in normal sleep and resting athletes. Nevertheless, researchers and practitioners usually equate hypertension with effective cardiac function and tissue perfusion, and regard hypotension as a harbinger of disaster.

Hemodynamic physiology is customarily explained by autonomic innervation that regulates cardiac inotropy and arteriolar diameter, but this explanation is weak. Were this true, the blood pressure force would appear simultaneously and equally throughout the arterial tree, for blood, like water, is incompressible. Instead, it appears as a traveling wave that generates lateral forces that vary in accord with arterial length and diameter, blood viscosity, red cell mass, and temperature. Furthermore, chronic hypertension causes sustained increases in cardiac work that induces congestive heart failure, and vascular smooth muscle contraction is energy-intensive, limited in duration, and soon followed by obligatory relaxation. Thus, neither cardiac inotropy nor vasoconstriction can readily explain sustained hypertension. In addition, exercise causes little change in the heart, but instead causes capillary proliferation that reduces vascular resistance and improves cardiac efficiency. The Capillary Gate Component (see above) provides a more efficient and effective explanation of hemodynamic physiology, because capillary surface area is vastly greater than that of all other vessels combined; capillary pressure, turbulence, and flow are minimal; and blood turbulence explains atherosclerosis, blood pressure, and the palpable pulse.
A more recent impediment to anesthesia theory is the argument that opioids promote cancer. This notion was inspired by recent studies that demonstrate prolonged survival of transplanted malignant tissues in the presence of opioid treatment, but there was no evidence of decreased longevity in the recipient animals, because they were prematurely sacrificed. Older studies in both humans and animals have demonstrated that cancer is not contagious, and that transplantation of malignant tissues to healthy individuals does not affect life span. Transplanted malignant tissue has never survived or induced cancer, with or without opioids. Furthermore, there is evidence that analgesia prevents cancer and reduces surgical complications. Nevertheless, these recent studies have discouraged opioid research and clinical use. This is unfortunate, because the ability of opioid analgesia to reduce cancer and heart disease when added to anesthesia has never been properly evaluated.

Perhaps the most subtle and pervasive factor frustrating anesthesia research and theory is carbon dioxide management. To appreciate this, one must understand the history of anesthesia. During the “Golden Era of Ether” anesthesia machines were equipped with “bypass valves” for CO2 supplementation. These valves enabled FICO2 supplementation that stimulated respiratory drive, increased cardiac output, enhanced tissue oxygenation, accelerated ether uptake, and reduced induction times. Unfortunately, these bypass valves enabled hazardous CO2 elevations that occasionally caused convulsions, cyanosis, and death. The valves disappeared after the danger was recognized, but anesthesiologists have subsequently regarded CO2 as a “toxic waste gas” that must be rid from the body. Pre-existing beliefs about CO2 toxicity have subsequently perturbed anesthesia research, as when Boniface and Brown exposed dogs to high levels of FICO2 and observed decreased cardiac work. They misinterpreted this as harmful myocardial toxicity, even though their own data demonstrated beneficial reductions in blood viscosity that provided the correct explanation.

With the introduction of curare, mechanical hyperventilation to prevent CO2 toxicity became a de facto “standard of practice” so that practitioners, researchers, and journal editors ignore its harmful effects. Hyperventilation persists despite abundant evidence of its hazards as well as the benefits of mild “permissive” hypercapnia, and the universal availability of capnography. Hyperventilation increases blood viscosity, which reduces cardiac output and decreases tissue and organ perfusion and oxygenation. It damages lung tissues, depletes CO2 tissue reserves, obtunds respiratory chemoreceptors, and undermines respiratory drive. It necessitates prolonged postoperative ventilator therapy when combined with effective opioid treatment. Hyperventilated patients breathe adequately after anesthesia provided opioids are judiciously minimized, but only because conscious awareness confers a form of respiratory drive that is independent of chemoreceptor function. However, occult chemoreceptor paralysis persists for hours, especially in geriatric patients, and causes unexpected respiratory arrest when patients are treated with seemingly innocuous doses of opioids and sedatives that promote sleep. The problem is known as “opioid hypersensitivity.” These misunderstood problems have perturbed opioid research and clinical utilization at the expense of patient comfort, safety, stress control, and theory development.

Meanwhile, critical care specialists re-discovered the clinical benefits of carbon dioxide more than 30 years ago. They routinely utilize “permissive hypercapnia” outside the operating room to prevent lung damage, reduce blood viscosity, increase cardiac output, improve tissue perfusion, and protect organ function. Mild hypercarbia conserves CO2 tissue reserves, preserves respiratory chemoreceptor function, enhances respiratory drive, accelerates opioid clearance, and enables effective opioid analgesia without necessitating prolonged respiratory support.

**Anesthesia and Stress Theory**

Selye’s ideas provided the most promising hope for a theory of anesthesia in the recent past. They imply that surgery induces stress mechanism hyperactivity that causes the “surgical stress syndrome.” This consists of pathological symptoms that appear distant from the time and location of surgery,
including fever, tachycardia, hypertension, mental disorders, myocardial infarction, stroke, malignancy, heart disease, allodynia, inflammation, edema, bowel ileus, and so forth. Selye’s theory further implies that the benefits of anesthesia derive from its ability to prevent stress mechanism hyperactivity, and that anesthesia technique can be modified to optimize surgical outcome.

The introduction of halothane and curare coincided with Selye’s ideas, and these developments produced an era of ferment, change, and stress-related anesthesia research that lasted roughly from 1960 to 1990. This brought an end to the “Golden Age of Ether” and inspired new ideas, equipment, and improvements in anesthetic safety and surgical convenience. Explosive agents were eliminated. Mechanical ventilation, pulse oximetry, capnography, arterial cannulation, and invasive monitoring were introduced. A substantial body of evidence was accumulated that corroborated Crile’s observation that analgesia added to general anesthesia improves outcome. Opioids and local analgesics were commonly combined with general anesthesia to optimize surgical stress control. However, all these techniques required additional skill and time, or entailed increased difficulties, risks, and inconvenience, and no explanation of their benefits could be found. Without a theory that explains the confusing and overlapping effects of anesthesia and analgesia, they have been largely abandoned.

Ironically, critical care practitioners re-discovered the benefits of “permissive hypercarbia” only a few years after the end of the era of anesthesia stress research. Capnography was simultaneously implemented as a means to detect lethal esophageal intubation and cardiac arrest, but its ability to safely enable the benefits of mild hypercarbia during anesthesia has yet to be appreciated. It is unfortunate that the era of anesthesia stress research occurred at a critical juncture when the benefits of hypercarbia during anesthesia were recently forgotten, mechanical hyperventilation had become a de-facto standard of practice, and capnography remained a rare and expensive research tool. Mechanical hyperventilation causes “opioid hypersensitivity” that precludes generous opioid administration without prolonged “weaning” from mechanical ventilation. Entrenched dogma thus precluded the development of a practical and safe opioid-based anesthesia technique that inhibits surgical stress. However, there is growing anesthesia awareness of the dangers of mechanical hyperventilation and the benefits of mild hypercarbia. Perhaps it is only a matter of time before the full potential of capnography is utilized to enhance patient comfort, mitigate morbidity, reduce mortality, encourage stress theory, and revolutionize anesthesia.

The recent discovery of the SRM enables the long-sought theory of anesthesia and analgesia that enables the alteration of anesthesia technique to optimize surgical outcome, and it promises the next significant advance in surgical safety and patient comfort. The SRM explains the Surgical Stress Syndrome. Surgery simultaneously and synergistically activates all three SRM pathways, causing positive feedback in accord with the duration and degree of surgical tissue disruption and surgical nervous stimulation. This manifests as symptoms distant from the location and time of surgery. 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, but outcome is substantially enhanced if synergistic combinations of anesthesia and analgesia are maintained continuously throughout surgery to minimize positive feedback caused by capillary gate component activation. Such combinations beneficially minimize positive feedback. They reduce blood viscosity and coagulability, improve tissue perfusion and oxygenation, protect organ function, enhance cardiac efficiency, reduce blood pressure, increase ejection fraction, slow heart rate via the Starling Mechanism and minimize fever, tachycardia, hypertension, dysrhythmias, infarction, mental confusion, malignancy, heart disease, and other manifestations of positive feedback in the aftermath of surgery.

Many anesthesiologists deliberately employ multiple hypnotic medications based on the belief that anesthesia involves multiple drug receptors, and each hypnotic agent controls a different receptor. The SRM explains why this polypharmacy increases toxicity, undermines predictability, and confers no benefit. Only one anesthetic and one analgesic, continuously maintained during surgery, are necessary to
control the capillary gate component and optimize outcome. Their synergistic interaction enables reduced dosages of both, which minimizes toxicity and residual effects, improves predictability, and speeds emergence.

No medication or technique is presently available to control the Tissue Pathway. Theoretically, continuous control of the Spinal and Cognitive pathways plus neutralization of tissue factor released into blood during surgery should abolish the Surgical Stress Syndrome altogether.\(^{228, 234, 252, 500, 528, 570}\)

**Blood Pressure and Anesthesia Management**

The SRM explains why blood pressure is a confusing, counterintuitive, and counterproductive standard of anesthesia monitoring. Blood pressure does not directly measure the cardiac force that propels blood. Therefore, it is not directly related to cardiac contractility, cardiac output, tissue perfusion, tissue oxygenation, stress, anesthesia, and patient well being as commonly assumed. The heart is often regarded as the “Charles Atlas” of the body, but it more closely resembles a 90 lb weakling. The secret of mammalian is efficiency rather than power and force. Red blood cell morphology minimizes systolic flow resistance and enables the heart to move large quantities of blood with remarkable efficiency (see “Turbulence Mechanism” above). The force that propels blood is very weak, and barely adequate for brain perfusion. This explains why the head of most vertebrates is usually located a short distance above the heart. Exceptions to this rule, such as the giraffe, require a disproportionately large heart to propel blood to the brain.\(^{696}\) Brain perfusion can be compromised even though blood pressure appears adequate. This explains why the “sitting” or “beach chair” position is deceptively dangerous during surgery.\(^{697}\)

Before the onset of surgical stress, anesthesia induction inhibits the cognitive pathway, and blood viscosity declines. This alters blood turbulence in favor of turbulent mixing effects at the expense of turbulent lateral forces, and blood pressure declines. The subsequent onset of surgical stress activates the spinal pathway and increases blood viscosity and blood pressure despite effective anesthetic inhibition of the cognitive pathway. Based on the mistaken assumption that anesthetic agents possess analgesic properties, anesthesiologists traditionally employ anesthetic “overpressure” to control surgical hypertension. Unfortunately, anesthesia confers no benefit beyond its ability to inhibit the cognitive pathway. Instead, the toxic effects of anesthetic overpressure harmfully reduce cardiac contractility, which reduces diastolic turbulent lateral forces, and blood pressure declines. This creates a hazardous combination of depressed cardiac contractility, increased blood viscosity, and capillary hemostasis (capillary gate closure) that impairs cardiac output and tissue perfusion. Under these circumstances, hypotension is a harbinger of impending disaster.

Occult spinal pathway nociception also causes “wind up” syndrome during surgery that produces problematic muscle tension and unexpected movements. Anesthesia cannot prevent these problems. Muscle relaxants control the symptoms of wind up syndrome, but do not inhibit the cause, and occult spinal pathway nociception continues to release vWF and increase blood viscosity. This spinal pathway activity becomes acutely problematic during anesthetic emergence, when the restoration of conscious awareness causes a sudden increase in capillary gate component activity that increases the risk of infarction\(^ {552, 565}\). Meanwhile, tissue factor is released into systemic circulation by surgery. This activates the tissue repair component, which interacts with the capillary gate component to induce positive feedback that does not reach peak intensity for several hours after surgery.\(^ {17, 18}\) Combinations of anesthesia and analgesia that effectively control the capillary gate component can minimize this positive feedback and mitigate the symptoms of the surgical stress syndrome. Unfortunately, there is no presently available means to inhibit the tissue repair component, so surgical stress cannot be completely abolished. However, the SRM indicates that directed pharmaceutical research should be able to develop a safe and effective antidote for tissue factor in blood circulation that would enable the complete elimination of surgical stress.
Anesthesia practitioners often employ fibrinogenic pharmaceuticals to maintain blood pressure at “awake” levels in the misguided belief that this maintains tissue perfusion; instead, these drugs exaggerate blood pressure at the further expense of tissue perfusion and oxygenation. Many practitioners administer crystalloid and colloid solutions to maintain blood pressure and tissue perfusion, but this elevates blood pressure by altering blood turbulence in favor of turbulent lateral forces at the expense of turbulent mixing. This harmful effect soon dissipates when crystalloids and colloids diffuse into extravascular tissues.

In contrast, the addition of analgesia to anesthesia produces a genuine low stress state comparable to natural sleep that is counter intuitively characterized by mild hypotension and bradycardia. This prevents stress hormone release, reduces sympathetic tone and blood viscosity, promotes cardiac efficiency and tissue perfusion, protects organ function, prevents infarction, discourages infection, inhibits atherosclerosis, and minimizes positive feedback that causes malignancy and heart disease in the distant aftermath of surgery.

**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 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 reduces blood turbulence below a threshold, whereupon spontaneous systemic coagulation suddenly begins. This rapidly consumes and depletes coagulation enzymes and precursors and distorts the coagulation process. Thrombin converts fibrinogen to soluble fibrin, which depletes fibrinogen. 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. Factor XIII installs “cross-links” of fibronectin and plasminogen to soluble fibrin to generate insoluble fibrin, and this consumes both Factor XIII and fibronectin. Shortages of Factor XIII and fibronectin cause soluble fibrin to accumulate to excessive blood levels. Fibronectin exhaustion also causes Factor XIII to produce defective forms of insoluble fibrin with inadequate fibronectin “cross-links.” These imbalances cause soluble fibrin to form abnormal attachments to the pathological clots to produce “microthrombi.” Soluble fibrin also deposits on arterial walls. The abnormal coagulation activity reduces circulating red cell mass, which exaggerates blood turbulence and further inhibits effective coagulation. These abnormalities characterize DIC.

DIC most often occurs in patients who undergo extensive surgical intervention in the immediate aftermath of major trauma and massive blood loss. Trauma and surgery both release tissue factor into systemic circulation and increase Factor VII activity, causing SRM hyperactivity and positive feedback. 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 alter blood turbulence and dilute coagulation precursors and enzymes. DIC removes red cells from circulation, causing anemia that exaggerates blood turbulence and inhibits coagulation. Blood transfusion corrects the anemia, reduces blood turbulence, and increases blood coagulability, but excessive transfusion with washed, packed red cells devoid of plasma 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 increases blood viscosity.
Hypothermia activates the SRM and increases blood levels of insoluble fibrin, which also increases blood viscosity. Severe hypothermia impairs SRM enzymes, and inhibits hemostasis. Metabolic acidosis and hypothermia synergistically impair hemostasis.

**Eclampsia and Amniotic Fluid Embolus**

Like DIC, ARDS, MOFS and malignancy, eclampsia is a manifestation of SRM hyperactivity caused by combinations of stresses that stimulate the three pathways of SRM activity. Normal pregnancy is a stressful condition characterized by elevated blood levels of Factor VIII and insoluble fibrin that increase blood viscosity and coagulability. This is partially offset by Hemodilution that increases blood turbulence. Stressful conditions such as diabetes, obesity, and sepsis (commonly caused by occult urinary tract infections during pregnancy) can increase the risk of eclampsia by elevating SRM hyperactivity above the level of normal pregnancy. Eclampsia increases the risk of DIC, especially in the presence of amniotic fluid embolus. Amniotic fluid contains large concentrations of tissue factor, so that amniotic fluid embolus causes a sudden increase in Factor VII activity. When this occurs in the presence of pre-existing Factor VIII hyperactivity, it causes blood viscosity and coagulability to suddenly rise above the critical threshold where (DIC) begins.

**Sickle Cell Anemia**

Sickle cell anemia is caused by a structural weakness in red blood cells that renders them unable to withstand the physical stresses induced by pulsatile blood turbulence. Biconcave mammalian red blood cells spontaneously form “aggregate patterns” during systolic acceleration that inhibit systolic turbulent flow resistance. This explains how the mammalian heart efficiently accelerates blood from 0 to 125 cm/S and ejects its contents in a tenth of a second. As diastolic deceleration disintegrates aggregate patterns, the kinetic energy of speeding blood converts to a burst of turbulent energy that moves rapidly proximal to distal, halting blood flow as it moves and generating lateral forces that account for blood pressure and the palpable pulse. It simultaneously generates turbulent mixing forces that mobilize particulate deposits from the inner walls of arteries to retard atherosclerosis.

Blood levels of insoluble fibrin fluctuate in accord with stressful stimuli that activate the capillary gate component. Insoluble fibrin binds to red cells and interferes with the formation of aggregate patterns during systole, which increases systolic blood turbulence and subjects the red cells to exaggerated turbulent forces as they are accelerated during systole. Insoluble fibrin also alters the balance between turbulent mixing forces and turbulent lateral forces during the burst of turbulence that subsequently occurs during diastole. These turbulent forces do not harm normal red blood cells, but they damage the structurally weak red cells of sickle cell patients. The turbulent forces induced by insoluble fibrin explain how stress causes the sudden “sickling” phenomenon. It likewise explains why Sickle Cell crises affect blood levels of d-Dimer (Fibrin Split Products) and why long-term treatment with anticoagulants reduces the severity and frequency of Sickle Cell Crises. Opioids mitigate the Sickle Cell crisis by minimizing capillary gate component activity and reducing blood levels of insoluble fibrin.

**Pharmacology and the SRM**

In 1965, Holdemans reported that all “vasoactive” drugs increase fibrin turnover, and that “vasoconstrictors” cause greater fibrin turnover than “vasodilators.” The significance of these observations remained unappreciated in the absence of a logical explanation.

The effects of vasoactive drugs are generally attributed to drug-induced vascular smooth muscle contraction and relaxation that regulates vascular flow resistance. However, this explanation is illogical, because the ability of vascular smooth muscle to sustain contraction is energy-intensive, limited in
duration, and soon followed by obligatory relaxation, so that it cannot explain sustained elevations of vascular resistance such as occurs in essential hypertension. The capillary gate component provides an improved explanation of these effects. “Vasconstrictor” drugs promote fibrinogenesis (insoluble fibrin generation) that elevates blood viscosity, closes the capillary gate, decreases tissue and organ perfusion, and increases diastolic turbulent lateral forces at the expense of turbulent mixing. Fibrinogenic drugs therefore increase systemic vascular resistance and blood pressure, accelerate atherosclerosis, and increase blood coagulability. “Vasodilator” drugs promote fibrinolysis (the disintegration of insoluble fibrin) that opens the capillary gate, reduces blood viscosity, enhances tissue and organ perfusion, and increases turbulent mixing at the expense of turbulent lateral forces. They reduce systemic vascular resistance and blood pressure, inhibit atherosclerosis, and decrease blood coagulability. The terms “vasoconstrictor”, “vasodilator”, and “vasoactive” are therefore misnomers, for they suggest an explanation that is at odds with known facts. Drugs that affect vascular resistance are better described as “fibrinogenic” and “fibrinolytic.”

Ca+ levels affect thrombin activity that is essential for fibrinogenesis. Low Calcium levels inhibit thrombin activity, and thereby interfere with both the generation and the stabilization of insoluble fibrin, which impairs capillary hemostasis and clot formation, and causes bleeding. Trisodium citrate and EDTA bind strongly to Calcium and halt fibrinogenesis, and are used for blood preservation. Their effects are reversed by the addition of Calcium. Calcium chloride and calcium gluconate elevate serum Ca+ levels, increase thrombin activity, promote fibrinogenesis, close the capillary gate, and cause sharp but short-lived increases in systemic vascular resistance that increase BP and reduce Cardiac Index. Nitroprusside (NTP) and nitroglycerine (NTG) exert their fibrinolytic effects by releasing Nitric Oxide from the Vascular Endothelium that binds to Calcium and reduces thrombin activity.

MgSO4 competitively inhibits Calcium and promotes fibrinolysis. It prevents stent thrombosis, reduces mortality after myocardial infarction, offsets the hypercoagulability of blood caused by rapid crystalloid infusion, and mitigates the manifestations of eclampsia by inhibiting the generation of soluble fibrin that disrupts organ function.

Beta-blockers, Furosemide, and “Calcium Channel Blocker” drugs such as Nifedipine and Verapamil all have fibrinolytic properties that are best explained by their ability to bind Ca+. Their beneficial effects may best be explained by their ability to reduce both pulmonary and systemic vascular resistance and improve cardiac efficiency and organ perfusion. Calcium channel blocker drugs also inhibit platelet activity, promote bleeding, and improve pulmonary hypertension (especially when combined with “anticoagulant” medications), and these effects can be explained by their ability to inhibit thrombin activity.

Vasopressin promotes beneficial fibrinolysis by activating plasmin.

Epinephrine releases von Willebrand’s Factor from the Vascular Endothelium to induce capillary fibrinogenesis and capillary gate closure, and this explains how it increases systemic vascular resistance and Blood Pressure. Astrocytes protect brain perfusion from epinephrine effects, which explains why the use of epinephrine during cardiac arrest does not cause brain damage.

Salicylates exert their anti-inflammatory and anti-platelet effects by interfering with thrombin generation. Glucocorticoids inhibit the cellular effects of thrombin. Anticoagulant medications have no direct effect on vascular smooth muscle, but they interfere with thrombin production and fibrinogenesis, and this explains how they inhibit atherosclerosis, mitigate hypertension, and prevent sickle cell anemia crisis.

The effects of local anesthetics are explained by their ability to block the function of exposed Sympathetic nerve endings that directly innervate the Vascular Endothelium in addition to their ability to block nerve conduction. They block the sympathetic nerve endings that induce the release of von Willebrand’s Factor from the vascular endothelium, and inhibit the capillary gate.
component. Local anesthetics increase capillary flow and reduce coagulability and surgical stress whether administered via intravenous, tissue infiltration, epidural or spinal routes. When administered intravenously they reduce blood coagulability, bronchial hyper-reactivity, and surgical stress. When infiltrated into tissues they increase capillary flow and inhibit capillary hemostasis.

Sildinafil mimics parasympathetic activity by releasing nitric oxide from the vascular endothelium to promote capillary fibrinolysis and organ and tissue perfusion. This explains why it safely synergizes the effects of nitroglycerin, enhances organ transplantation, increases peristalsis, and treats High Altitude Pulmonary Edema (HAPE), pulmonary and systemic hypertension, congestive heart failure, diabetes, achalasia as well as erectile dysfunction.

The ability of Angiotensin Converting Enzyme (ACE) inhibitors to control hypertension is attributed to their effects on angiotensin, but is best explained by their reduction of von Willebrand Factor levels. The reduction of von Willebrand Factor explains how they increase cardiac output and reduce systemic vascular resistance, why they cause unpredictable tissue edema and swelling that is analogous to angioneurotic edema, and why they are contra-indicated in patients with aortic valve replacements and aortic outflow obstruction.

The SRM indicates that fibrinolysis and thrombin inhibition should improve outcome in organ transplantation, spinal injuries, burns, ARDS, MSOF, and malignancy.

Infarction

The presently prevailing explanation of infarction is plaque disruption that releases debris, obstructs distal flow, and initiates destructive thrombus formation. This hypothesis does not explain myocardial infarction that occurs during anesthetic emergence that does not involve thrombus formation and is prevented by analgesia. It likewise fails to explain the “no-reflow” phenomenon, wherein stent installation restores arterial flow but fails to restore capillary perfusion in infarcted tissues. It also fails to explain why infarction symptoms, autonomic imbalance, and microvascular flow disturbances appear long before thrombus formation; why anticoagulants must be administered before thrombus formation to prevent myocardial damage; and why opioids, which have no anticoagulant properties, mitigate infarction symptoms and severity.

The reductions in systemic vascular resistance and blood pressure that accompany successful treatment with anticoagulants such as streptokinase and urokinase remain unexplained, as anticoagulants do not affect muscular vasculature. The simplest explanation of early stages of myocardial infarction is that capillary gate hyperactivity inhibits tissue perfusion and oxygenation, causing a vicious cycle of angina that elevates SNS activity and aggravates capillary gate closure in the affected tissues. The beneficial effects of anticoagulants are best explained by rapid fibrinolysis that opens the capillary gate, restores capillary perfusion to infarcted tissues, and reduces systemic vascular resistance and blood pressure.

Tissue Plasminogen Activator (TPA) has largely supplanted urokinase and streptokinase as treatments for acute infarction. It causes less dramatic reductions in systemic vascular resistance and blood pressure, but it is probably less potent as a treatment, because it only indirectly accelerates the disintegration of insoluble fibrin by increasing plasmin activity.

Opioids lack direct effects on either muscular vasculature or coagulation; they mitigate myocardial infarction damage via their ability to control infarction angina, reduce SNS tone and activity, open the capillary gate, and restore perfusion in afflicted tissues.

The ability of “statin” drugs to prevent myocardial infarction can best be explained by their ability to lower VWF levels, inhibit insoluble fibrin generation, reduce viscosity, retard atherosclerosis.
and promote capillary perfusion. However, these drugs undermine capillary gate function and can cause lethal angioneurotic edema.

Nitroglycerin and Nitroprusside prevent angina and infarction by releasing nitric oxide from the vascular endothelium, which opens the capillary gate (see above).

The exaggerated vulnerability of geriatric patients to infarction is caused by capillary senescence that compromises tissue and organ perfusion. This is reflected by the presence of capillary bed “filling defects” in healthy geriatric patients.

**Rheumatoid Disease**

Rheumatoid disease is usually attributed to “autoimmune” activity, but the cause is unknown. SRM dysfunction that generates amyloid protein explains these diseases. Amyloid deposits are universally present in afflicted organs and tissues in rheumatoid disease. Rheumatoid nodules consist of amyloid deposits. Amyloid deposits are present in 90% of Type II diabetics, and they destroy pancreatic islet cells. Lymphomas and diabetes cause amyloid tumor formation. Amyloidosis explains the symptoms and relationships of Rheumatoid Diseases, Diabetes, Parkinson’s disease, vitamin D depletion, and infectious “prions”. Surgery and other forms of stress aggravate amyloidosis.

Fibrillar Actin protein interacts with insoluble fibrin, and disrupts the tissue repair function of the viscoelastic clot. This causes a “vicious cycle” that consumes and depletes Factor X and Vitamin D, accelerates atherosclerosis, and generates amyloid protein that forms disruptive deposits in organs and tissues.

Amyloidosis is a disorder of protein conformation caused by “misfolding” in which normally soluble proteins are deposited extracellularly as insoluble fibrils that impair tissue structure and function. Over 20 unrelated proteins form amyloid fibrils in vivo, with fibrils sharing a lamellar cross-beta sheet structure, composed of non-covalently associated protein or peptide subunits. Disorders of Actin metabolism cause the Actin molecule to undergo conformational changes to form amyloid protein.

Amyloidosis depletes Factor X, which disturbs clot permeability and disrupts tissue repair. Disturbances in clot permeability explain the chronic inflammation, cell proliferation, and increased immune cell activity observed in rheumatoid diseases. Amyloidosis causes bleeding by damaging blood vessels. Amyloid and/or Actin may increase blood viscosity and accelerate atherosclerosis by inhibiting the normal disintegration of insoluble fibrin, and this explains the strong associations between rheumatoid disease, diabetes, amyloidosis, and atherosclerosis.

Like insoluble fibrin, Actin is a “fibrillar” molecule that polymerizes into strands. It is the most abundant protein in the vertebrate body. It is present in all cells, and is released into the blood by cell damage. It becomes entangled with insoluble fibrin in the viscoelastic clot. It binds to the “kringle” portions of the plasmin molecule and inhibits plasmin activity that disintegrates the insoluble fibrin molecule into Fibrin Split Products. It thus interferes with the normal disintegration of insoluble fibrin by plasmin, which disturbs clot permeability, blood viscosity, and tissue repair. Actin triggers a “vicious cycle” that generates amyloid protein, consumes Factor X, depletes vitamin D, and accelerates atherosclerosis. This explains the close associations between and among amyloidosis, atherosclerosis, Alzheimer’s disease, rheumatoid arthritis, Systemic Lupus Erythematosis, diabetes, Parkinson’s disease, infectious “prion” release, inflammatory bowel disease, and other pathologies. Actin that is released from damaged red blood cells during bypass surgery explains SIRS that is observed in these patients.

Gelsolin and vitamin D neutralize Actin and its effects. Actin is metabolized in two stages. In the first stage, the fibrillar Actin molecule is rapidly reduced to inert subunits by the
blood enzyme gelsolin. Gelsolin binds avidly to fibronectin, so that it becomes concentrated in the viscoelastic clot. Thrombin energizes gelsolin. In the second stage, Actin subunits are metabolized in a slower reaction that consumes vitamin D. This explains why depletion of gelsolin and Vitamin D aggravates the chronic inflammatory effects and exaggerated immune activity that occur in rheumatoid diseases as well as in the aftermath of cardiopulmonary bypass (Systemic Inflammatory Response Syndrome), major surgery (Surgical Stress Syndrome), severe injury (Multi-Organ Failure Syndrome) and sepsis.

**Hypertension And Diabetes**

Essential hypertension (EH) is elevated blood pressure of unknown cause that increases the risk for cerebral, cardiac, and renal events. It begins with unexplained proteinuria and insulin resistance, while blood pressure remains deceptively normal at rest, but increases to unexpected levels during exercise and emotion. As the disease progresses, blood pressure eventually remains continuously elevated even at rest, and organ failure ensues. Pre-eclampsia patients exhibit similar progression from occult proteinuria and insulin resistance to overt hypertension.

Essential hypertension is usually attributed to arteriolar “stiffness,” reductions in the caliber and number of arterioles, and impaired arterial compliance. This explanation fails to explain glucose intolerance and elevations of VWF, D-dimer (“Fibrin Split Products”), insoluble fibrin, Factor VII and Factor VIII activity, increased blood viscosity and coagulability, systemic inflammatory effects, and accelerated atherosclerosis that occurs in both systemic and pulmonary forms of hypertension. It also fails to explain how hypertension increases the risk of stroke and myocardial infarction, because these pathologies are paradoxically thrombotic rather than hemorrhagic. Hypertension can be successfully treated with anticoagulants, and successful treatment is characterized by reductions in VWF levels. The hypercoagulable state also explains the association between essential hypertension, amyloidosis, and accelerated atherosclerosis, none of which are explained by stiffness, impaired compliance, and reduced arteriole numbers.

The SRM explains essential hypertension and diabetes and their close relationships. Direct parasympathetic innervation opens the capillary gate in visceral organs by releasing nitric oxide from the vascular endothelium. Parasympathetic stimulation also releases insulin from the pancreas into flowing blood. Insulin releases nitric oxide from capillary walls and opens the capillary gate in peripheral tissues that lack direct parasympathetic innervation. This explains why insulin prolongs bleeding time, reduces systemic vascular resistance, increases cardiac index, aggravates angina, and counteracts “vasopressor” (fibrinogenic) drugs; why allostatic load inhibits insulin effects; and why diabetes and hypertension are closely related.

Nitric oxide is also bactericidal, so that PNS activity inhibits infection as well as enhances tissue perfusion and oxygenation.

Capillary beds naturally deteriorate with age, and this increases both vascular resistance and insulin requirements. Both diabetes and hypertension involve accelerated capillary senility that increases vascular resistance (blood viscosity), elevates blood pressure, impairs tissue perfusion and glucose uptake, and increases insulin requirements.

Inadequate insulin release causes Type I diabetes. Type II diabetes is caused by accelerated capillary senility that impairs glucose uptake in peripheral tissues and increases insulin requirements. This explains why Type II diabetes occurs in older persons. Chemical destruction of sympathetic nerve endings in the pancreas has cured Type I diabetes in a rat model, which refutes the hypothesis that autoimmune activity causes diabetes.

Environmental and chemical stress accelerates both capillary senility and atherosclerosis, and aggravates both diabetes and hypertension. Emotional stress, such as earthquakes and job stress, accelerates both atherosclerosis and capillary senility by increasing SNS activity that elevates
blood viscosity 531-533, 563. For example, Carroll Shelby of car racing fame employed nitroglycerin treatment to sustain his emotionally stressful career, and ultimately underwent heart replacement surgery twice 417. The baboons used by NASA for rocket sled tests developed hypertension and died prematurely 818. Uninjured earthquake victims exhibit infarctions, strokes, and elevations of blood pressure, von Willebrand Factor, Factor VIII, blood viscosity, and blood coagulability that persist for months 293, 556, 557.

The simplest explanation is that emotional and environmental stress causes occult SRM hyperactivity that generates thrombin, soluble fibrin, and insoluble fibrin. Thrombin causes inflammatory effects. Soluble fibrin causes proteinuria. Insoluble fibrin increases blood viscosity. Their combined effects insidiously undermine organ function, accelerate atherosclerosis and capillary senility, and increase insulin requirements and vascular resistance 311, 351, 352, 354, 379, 381, 384-386, 390. In the early stages, exercise increases cardiac output and emotional stress exaggerates pre-existing abnormal flow resistance, so that both cause exaggerated elevations of blood pressure. Blood pressure and insulin resistance gradually increase as the disease progresses. Chronically increased blood viscosity increases cardiac work and deteriorates cardiac performance, and it inexorably induces cardiomyopathy that is characterized by myocyte hypertrophy, extracellular collagen deposition, and increased cardiac wall thickness. Ultimately the heart suddenly “balloons” in size, cardiac walls become thin, and overt congestive heart failure ensues 165, 174-176, 313, 352, 379, 384.

Athletic Conditioning

Exercise conditioning produces several unexplained beneficial effects 346, 347. It ameliorates the pathological effects of chronic hypertension, coronary artery disease, atherosclerosis, and diabetes 36, 312, 348. It produces resting bradycardia and reduced blood pressure that is usually attributed to increased vagal tone, but this explanation is weak 35, 36. Capillary gate operation offers an improved explanation for exercise conditioning. Exercise increases SRM activity 349. It induces both arteriogenesis (collateral vessel enlargement) and angiogenesis (capillary proliferation) in the muscles that are subjected to regular exercise, and this reduces Systemic Vascular Resistance (blood viscosity) 31, 34, 51, 550. The reduction in Systemic Vascular Resistance lowers blood pressure at rest, when metabolic demands and nervous stimulation of the cardiovascular system are both minimal, and facilitates increased Ejection Fraction, so that Heart Rate is reduced in accord with the Frank-Starling principle. The alleviation of hypertension is also explained by the reduction in Systemic Vascular Resistance. The improvement in diabetes is explained by the angiogenesis in skeletal muscle that improves muscle cell exposure to glucose and facilitates glucose uptake 351-354.

Organ Function and the Capillary Gate

Autonomic balance governs organ function by controlling organ perfusion. SNS activity “closes” the capillary gate, reduces organ perfusion, and decreases organ function; while PNS activity “opens” the capillary gate, increases organ perfusion, and enhances organ function 226, 238. Parasympathetic activity increases capillary flow in lung 819 that can cause capillary engorgement that manifests as “bronchoconstriction”. It increases brain blood flow in accord with brain activity 331, 333, 376. In enhances esophageal peristalsis 743, which decreases food transit time 283, 284, 745. It increases saliva production by enhancing salivary gland perfusion 329. It in creases penis perfusion to enable erection 288, 289. It increases intestinal peristalsis and digestive fluid production 332, 375. It increases the activity of Beta Cells and the release of insulin from the pancreas. SNS activity opposes all these PNS effects by closing the capillary gate. Severe increases in SNS tone can cause death from myocardial infarction or stroke by disrupting the perfusion of these vital tissues 219, 222, 226, 293.

Direct SNS innervation is present throughout all body tissues, but direct PNS innervation is limited to internal organs 238. Insulin primarily affects peripheral tissues that are devoid of PNS innervation, such as skeletal muscle 57. It opens the capillary gate by releasing nitric oxide 379, 396, 399, and
organ transplant, pneumonia, a wide variety of malignancy tissue maintenance, and is dangerous. They prevent infarction and retard atherosclerosis. Their activity is needed, such as asthma, diabetes, and tissue factor that is essential for thrombomodulin. They release von Willebrand’s Factor and increases Systemic vascular Resistance in accord with SNS activity, does not ordinarily cause brain damage when used in medical emergencies. Astrocyte activity also explains the abundance of tissue factor in brain tissue that is necessary to supplement capillary hemostasis in brain tissues. Severe head injuries release tissue factor into systemic circulation, which increases morbidity and mortality. Sildenafil is a recently introduced drug that appears to have the unique ability to mimic the effects of the PNS. It releases nitric oxide and promotes organ function in capillary beds in the same manner as Parasympathetic stimulation. It releases nitric oxide and facilitates glucose uptake. This explains why insulin causes a prolonged bleeding time, reduces Systemic Vascular Resistance, increases Cardiac Index and Stroke Index about 20 minutes after a meal, and opposes the effects of “vasopressors”. This explains why insulin causes a prolonged bleeding time, reduces Systemic Vascular Resistance, increases Cardiac Index and Stroke Index about 20 minutes after a meal, and opposes the effects of “vasopressors”.

Astrocytes release nitric oxide and Thrombomodulin in response to PNS stimulation to protect oxygen-sensitive brain tissue from the harmful effects of capillary hemostatis. They proliferate in the presence of thrombin elevations. Their presence explains why brain tissue bleeds readily. It also explains why epinephrine, which releases von Willebrand’s Factor and increases Systemic vascular Resistance in accord with SNS activity, does not ordinarily cause brain damage when used in medical emergencies. Astrocyte activity also explains the abundance of tissue factor in brain tissue that is necessary to supplement capillary hemostasis in brain tissues. Severe head injuries release tissue factor into systemic circulation, which increases morbidity and mortality.

Medical Treatments for Stress-Related Pathologies

SRM hyperactivity can be lethal, and it is stubbornly resilient because of its redundant, synergistic pathways. For example, the worldwide influenza epidemic of 1918 killed millions of young, healthy victims but paradoxically spared the very young, the very old, and the weak. Similarly, asthma afflicts young, healthy victims who generate excessive soluble fibrin in airway passages exposed to inhaled antigens. Control of the SRM can improve outcome in these and numerous other conditions, including severe burns, MOFS, ARDS, eclampsia, acute spinal cord injury, acute brain injury, and so forth.

Treatments for many forms of SRM activity have long been available, but their effective use is hampered by the lack of effective theory that explains how and why they work, and how they can best be applied.

Heparin and Plavix inhibit Factor VIII but do not interfere with the interaction of Factors VII, X and tissue factor that is essential for tissue maintenance, tissue repair, and embryological development. They are thus relatively safe for use in pregnant women, surgery patients, and for prolonged treatment to prevent infarction and retard atherosclerosis. In contrast, warfarin interferes with the interaction of Factors VII, X and Tissue Factor, so that it disrupts embryological development, wound healing and tissue maintenance, and is dangerous when used for prolonged treatment. For the same reason, it inhibits malignancy, which involves tissue repair hyperactivity.

Trisodium citrate and MgSO4 inhibit thrombin activation by Ca+, so that they could be useful in a wide variety of situations where acute reduction in SRM hyperactivity is needed, such as asthma, pneumonia, influenza, eclampsia, mis-matched blood transfusion, acute spinal cord injury, infarction, organ transplants, severe burns, ARDS, MOFS, and malignancy.
Sildinafil mimics the effects of PNS activity and promotes organ function in a wide variety of conditions by releasing NO from the vascular endothelium. It thus provides an effective treatment for High Altitude Pulmonary Edema, achalasia, digestive disorders, diabetes, and hypertension as well as sexual dysfunction.

Pharmaceutical research to develop safe treatments that neutralize tissue factor in blood circulation or mimic the effects of stoichiometric ATIII, Protein C, and Tissue Factor Pathway Inhibitor would undoubtedly be useful. The addition of fibrinogen, fibronectin, and vitronectin to intravenous fluids should improve their safety and effectiveness. Non-invasive monitors of blood viscosity would provide a useful means to detect SRM hyperactivity during and after surgery.

**Evolution, Embryology and the SRM**

Most DNA information derives from prokaryotic (i.e. bacterial) cell research. Prokaryotic cells are easy to study. They 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 free in the cytoplasm and transmits its genetic information via a straightforward mechanism that employs RNA templates to generate proteins.

Multi-cellular animals consist of eukaryotic cells that are vastly more complex than prokaryotic cells. They utilize mitochondria for respiration, which enables them to become much larger, assume diverse shapes, and build complex multicellular life forms. Their internal structure is complex. Their DNA is enclosed within a nucleus in the form of chromosomes that divide when the cell replicates. Their cytoplasm contains structurally distinct “organelles” with specific functions. Many of these organelles have their own DNA that replicates independent of the nuclear DNA. Eukaryotic cells are thus believed to have originated when a “parent” cell somehow engulfed other types of previously free-living single-cell organisms that subsequently became symbiotic organelles. The nuclear membrane of the parent cell isolates its DNA from the cytoplasmic DNA of the organelles.

The nuclear DNA of complex animals transmits its genetic information via mechanisms that are not yet fully understood. It 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 initially assumed to have no function, but recent research reveals that it consists at least in part of “introns” that somehow control stem cell maintenance, cell proliferation, and apoptosis to enable embryological tissue development. However, the introns do not produce proteins. These observations have led the current generation of cell researchers to hypothesize that “junk” DNA transmits its information via an unknown cytoplasmic mechanism to enable embryological development 58, 822-824.

The previous generation of stress researchers held a similar viewpoint. They knew that the DNA mechanism does not explain embryological development. They believed that the stress mechanism postulated by Hans Selye acts as a “companion mechanism” that works closely with DNA to convert genetic information into cell proliferation and differentiation to generate embryological structures, and that the stress mechanism remains active throughout life to maintain and repair mature structures, while DNA itself becomes quiescent once embryological development is complete.

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 52, 106, 825. Mature cells have stable configurations of thrombin receptors that characterize their type, but cells can change their thrombin receptors during tissue repair and malignancy, and thereby alter their responses to thrombin. I hypothesize that introns regulate thrombin receptors at precise time intervals to govern cell proliferation and differentiation during embryological development, and that they release tissue factor to induce thrombin generation by the SRM to energize embryological development. Such a mechanism would explain how introns control three-dimensional cell proliferation, differentiation, apoptosis, and other cell activities necessary for structural development. It would explain why introns do not produce proteins, and why they...
remain quiescent once embryological development is complete, while the SRM remains active for the duration of life to maintain and repair mature structures. It would explain why defects in tissue factor and Factors VII and X and medications such as Coumadin and thalidomide that disrupt their function cause death or disruption during embryological development, while heparin and other anticoagulants that affect only Factor VIII do not disturb embryological development, because Factor VIII is not essential for embryological development.

The SRM appears to be highly conserved in nature, and it provides insight to the nature of evolution. The sudden appearance of the SRM/introns mechanism explains the “Cambrian Explosion” of complex animal forms some 540 million years ago, because it enables complex animal structures. It explains how DNA preserves genetic information that enables adaptation to environmental changes.

**Fresh Definitions Enabled by the SRM**

Definitions of stress-related phenomena remain imprecise because of the inability to explain them. For example, the International Association for the Study of Pain defines pain as “An unpleasant sensory or emotional experience associated with actual or potential tissue damage.” It defines analgesia as “Absence of pain in response to stimulation which would normally be painful” and it defines nociception as “The neural process of encoding noxious stimuli.” The American Institute of Stress states “Stress is difficult for scientists to define because it is a subjective sensation associated with varied symptoms that differ for each of us.” The SRM enables improved definitions as follows:

**Stress** is any force or stimulus that activates the SRM.

**Nociceptors** are nervous tissue disruption sensors in the skin and internal organs that activate the SRM in accord with mechanical, chemical, and thermal changes above a set threshold.

**Nociception** is nociceptor activation that stimulates increased Sympathetic Nervous System (SNS) activity via peripheral sensory nerves and spinal cord internuncial neurons that communicate with sympathetic ganglia. Nociception also communicates with the corticofugal structures in the brain that generate conscious awareness. Descending cortical pathways inhibit nociception pathways in the spinal cord. Nociception is effectively controlled by analgesia, but is ineffectively controlled by anesthesia in clinically safe and reasonable doses.

**Allostasis** is the automatic alteration of autonomic balance and the generation of rage, apprehension, and fear in accord with subconscious memories of prior sensory input. The brain maintains audiovisual, olfactory, emotional, and sensory memories of all waking moments. During sleep the memory recording process halts while the dreaming process compares, contrasts, exaggerates and suppressing existing memories so as to enhance the ability of vertebrates to pre-emptively recognize dangerous circumstances and facilitate “fight or flight”.

**Pain** is the perception of nociception by conscious awareness and/or a subconscious memory of nociception that represents a form of allostasis. The perception of pain can be exaggerated or minimized by emotional mechanisms in accord with subconscious memories of prior experiences as a manifestation of allostasis. Pain activates the SNS via hypothalamic pathways that are independent of spinal cord function, and this grossly exaggerates the SNS activity caused by nociception alone. Pain can be controlled either by analgesics that inhibit nociception or anesthetics that inhibit conscious awareness.

**Anesthesia** is the reversible inhibition of corticofugal and emotional mechanisms that generate conscious awareness. Anesthetic agents include intravenous drugs such as Propofol, alcohol, benzodiazepines, barbiturates, Etomidate, droperidol, ketamine, and volatile inhalation agents including Halothane, Ether, Ethrane, chloroform, cyclopropane, Isoforane, Desflurane, and Sevoflurane. All anesthetics are hypnotic agents that exert their benefits by inhibiting conscious awareness, which prevents SNS activation by fear and pain. Small doses of anesthetic agents can eliminate the perception of pain without completely abolishing conscious awareness. Ether readily illustrates this effect, because it has a
high blood/gas solubility coefficient and takes effect slowly. During the early onset of ether effects, patients lose the ability to perceive pain even though they continue to speak coherently. Greater doses of ether abolish conscious awareness altogether. Modern inhalation agents such as Isoforane have low blood/gas solubility coefficients and take effect so quickly that these nuances cannot be readily observed. However, neither ether nor any other anesthetic agent can inhibit nociception in safe and practical doses. Furthermore, anesthetic agents may indirectly exaggerate nociception by inhibiting descending brain pathways that suppress spinal cord pathways.

**Analgesia** is the inhibition of nociception. NSAID analgesics inhibit inflammation that activates nociceptors. Lidocaine, bupivacaine, and other “local anesthetics” (which should logically be called “local analgesics”) interfere with the function of peripheral sensory nerves and/or spinal cord pathways that transmit nociceptor signals to the SNS. Opioid analgesics inhibit nociception pathways in the spinal cord. By inhibiting nociception, analgesia eliminates the ability of conscious awareness to perceive pain, but it does not prevent other forms of sensation that are perceived by conscious awareness, including auditory, tactile, visual and olfactory stimuli that cause conscious awareness to activate the SNS via hypothalamic pathways even in the absence of nociception and pain. For example, a patient undergoing hernia repair under spinal analgesia may be frightened to death in the event that a fire or earthquake occurs during the surgery, because his perception of danger via sight, sound, vibration, and smell activates the SNS.

**Conclusion**

In his book “The Structure of Scientific Revolutions”, Thomas Kuhn describes how scientific progress occurs in a predictable pattern. Prolonged periods of “ordinary science” prevail during the intervals between scientific revolutions. During these quiet intervals, patient research toil produces fresh evidence that is perceived in terms of prevailing theory. As fresh information accumulates, inconsistencies appear that cannot be explained by the prevailing paradigm. Researchers employ strained and speculative rationalizations to explain these inconsistencies in terms of the prevailing paradigm, and new theories appear. Researchers, professors, and experts seldom propose important new theories. Instead, amateurs or persons working outside the specialty are the usual source of important new theories. Eventually there is a “paradigm shift” as large numbers of researchers, professors, and experts embrace a new theory that provides a better explanation of available evidence. Nevertheless, many adhere to the old paradigm long after most have embraced the new concept.

The discovery of DNA illustrates Kuhn’s principles. Before the discovery of DNA, most experts believed that proteins were the medium of genetic inheritance. Vernon Avery provided convincing evidence to the contrary, but prevailing opinion was little affected until Watson and Crick described the testable DNA mechanism. Both Watson and Crick were young amateurs with no research experience or formal training in cell biology. Watson was a graduate student in ornithology, and Crick was a mathematician who had participated in war research. They gleaned information from published reports and from x-ray diffraction photographs surreptitiously smuggled from the laboratory of Rosalind Franklin, a talented researcher. Crick utilized his mathematical expertise to calculate the angles of DNA atoms, and Watson employed this information to construct models of the DNA molecule. Their description of the DNA molecule was revolutionary, because it provided a convincing testable mechanism that explains how the DNA molecule stores and transmits genetic information. Nevertheless, many experts and researchers stubbornly adhered to the old belief that proteins are the medium of genetic inheritance long after the majority had embraced DNA theory.

Scientific history suggests that DNA theory has reached the limit of its utility, and will soon be either replaced or reinvigorated by a new scientific paradigm. DNA has dominated biological science and research for more than 60 years, but it has failed to explain either embryological development or adult biology. There is growing frustration with the lack of theoretical progress in the biological sciences.
Attempts to explain incompatible evidence in terms of the prevailing DNA paradigm have become strained, speculative, and complex. The Genome Project illustrates this failure. It promised to enable dramatic advances in medicine and biology. It cost billions of dollars and produced a complete description of the gene sequences in human and animal DNA as planned, but it failed to inspire even a single medical treatment.

Stress theory represents the most obvious successor to the DNA paradigm. The ability to explain disparate phenomena is the hallmark of effective theory, and stress theory has always offered the simplest (and therefore best) explanation of adult biology. It complements and extends DNA theory. It explains embryological development as well as physiology, pathology, and stress. It enables a Unified Theory of Medicine. It has never been refuted, and it remains as potent as ever. The SRM description remains crude, but it provides the long-sought mechanism needed to enable, test, and confirm stress theory, unleash its enormous promise, and introduce a new era of scientific progress.

Medicine is the most conservative of sciences, and change comes slowly. Nevertheless, it is now poised at the threshold of the most revolutionary advance in its venerable history. Once the SRM has been tested and confirmed, stress theory will transform medicine from an art based on experiment to a genuine science founded on theory. It will provide a universe of opportunities for research, pharmaceutical development, diagnosis, and treatment at least as vast as current practice, and it will introduce a new era of health, longevity, productivity, and freedom from the scourge of disease.