30 Years Lost in Anesthesia Theory

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Abstract The recent discovery of the "Stress Repair Mechanism" (SRM) enables the Unified Theory of Medicine postulated by Hans Selye. It confers cohesive theories of anesthesia, analgesia, and allostasis that enable the alteration of anesthetic technique to optimize surgical outcome. The SRM continuously maintains and repairs the vertebrate body in accord with stressful forces and stimuli. Three synergistic pathways activate the SRM: the spinal pathway, the cognitive pathway, and the tissue pathway. Emotional mechanisms modulate the cognitive pathway, which explains allostasis. Surgery simultaneously stimulates all three synergistic pathways, causing harmful SRM hyperactivity that manifests as the Surgical Stress Syndrome. Anesthesia inhibits the cognitive pathway. Analgesia inhibits the spinal pathway. Synergistic combinations of anesthesia and analgesia minimize SRM hyperactivity better than either alone. This principle improves outcome, simplifies anesthetic technique, and minimizes polypharmacy and drug toxicity. Once verified, stress theory will advance surgical safety, accelerate recovery, minimize complications, reduce costs, enhance patient comfort, and guide pharmaceutical development to discover treatments that inhibit the tissue pathway, and thereby eliminate surgical stress altogether.

Keywords: Unified Theory of Medicine, Hans Selye, stress mechanism, stress repair mechanism, surgical stress syndrome, anesthesia theory, analgesia, allostasis, atherosclerosis, apoptosis, nitric oxide, von Willebrand Factor, coagulation, tissue repair, hemodynamic physiology, Disseminated Intravascular Coagulation, eclampsia, crystalloid, colloid, vasoactive, vasopressor, vasodilator.

INTRODUCTION

Anesthesiology suffers for lack of a theory that enables the alteration of anesthesia to optimize surgical outcome. Invasive surgery causes a potentially lethal stress reaction and was avoided until anesthesia` provided a practical means to reversibly 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 during surgery. An effective theory must explain these problems.

Attempts to establish a 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 Robert Crile demonstrated that analgesia improves surgical safety in anesthetized patients [1]. This means that an effective theory must explain the confusing effects of both anesthesia and analgesia. However, most efforts have focused on anesthesia and neglected analgesia [2-4]. 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 [5].

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OBSTACLES TO EFFECTIVE ANESTHESIA THEORY

Pre-existing beliefs, entrenched habits, and defective standards are obstacles to anesthesia research, patient safety, and theory development. Most of these arose 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 eliminates conscious awareness. This conveyed the conviction that anesthesia has 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 [4].

Also problematic is the counterintuitive mystery of hemodynamic physiology. The nature of blood pressure and the palpable pulse has never been understood, and they became basic monitoring standards for lack of alternatives. Researchers and practitioners often equate hypertension with effective cardiac function and tissue perfusion, and fear hypotension as a harbinger of disaster. However, decreased cardiac output and tissue perfusion usually accompanies tachycardia and hypertension, while enhanced cardiac output and perfusion can occur despite bradycardia and hypotension, as in normal sleep and trained athletes at rest.

A more recent problem is evidence suggesting that opioids promote cancer. These studies demonstrate that opioid treatment prolongs the survival of malignant tissue transplanted into healthy animals, but there was no evidence of decreased longevity, because all the animals were

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sacrificed [6]. Older studies in both humans and animals have demonstrated that cancer is not contagious. Transplanted malignant tissue has never survived or induced cancer, with or without opioids. Furthermore, there is evidence that analgesia can prevent cancer and reduce surgical complications [7-9]. Nevertheless, these recent studies have obscured evidence that opioids reduce surgical risk, and discouraged opioid research and clinical use [8, 9]. This is unfortunate, for the ability of opioids added to anesthesia to reduce cancer and heart disease after surgery has not 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 often equipped with "bypass valves" for CO2 supplementation [10]. This stimulated respiratory drive, increased cardiac output, enhanced tissue oxygenation, accelerated ether uptake, and minimized induction times. Unfortunately, these bypass valves enabled extreme CO2 elevations that occasionally caused convulsions, cyanosis, and death [11]. The valves disappeared after the danger was recognized, but anesthesiologists have thereafter regarded CO2 as a "toxic waste gas" that must be rid from the body. Pre-existing beliefs about CO2 toxicity appear to have perturbed subsequent 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 [12].

With the introduction of curare, mechanical hyper-ventilation to prevent CO2 toxicity became a de facto "standard of practice" so that practitioners, researchers, and journal editors alike overlook its harmful effects. It persists despite abundant evidence of its hazards as well as the benefits of mild hypercapnia and the universal availability of capnography [13-16]. Its insidious effects confuse research and undermine safety. It 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 after generous opioid treatment. Hyperventilated patients breathe adequately after anesthesia if 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 reasonable doses of opioids and sedatives that promote sleep. The problem is known as "opioid hyper-sensitivity" [17, 18][1]. These misunderstood problems have caused researchers and practitioners to avoid opioid research and treatment at the expense of patient comfort, safety, stress control, and theory development.

Meanwhile, critical care specialists re-discovered the clinical benefits of carbon dioxide nearly 30 years ago. They routinely utilize mild "permissive hypercarbia" to prevent lung damage, reduce blood viscosity, increase cardiac output, and improve tissue and organ perfusion and oxygenation. Permissive hypercarbia conserves CO2 tissue reserves, preserves respiratory chemoreceptor function, enhances respiratory drive, accelerates drug and opioid clearance from the brain and other tissues, and enables increased opioid dosage without necessitating prolonged respiratory support.

ANESTHESIA AND STRESS THEORY

Stress theory represented the most promising hope for a theory of anesthesia in the recent past. It originated in 1951 when Hans Selye postulated the presence of a single physiologic "stress mechanism" that continuously maintains vertebrate structure [19]. He believed that this mechanism would enable a "Unified Theory of Medicine" that would explain embryological development, tissue repair, hemodynamic physiology, pathology, stress and their relationships. This simple idea inspired an intense international search for the stress mechanism that lasted more than 30 years, but the effort failed and was abandoned. Stress theory also inspired anesthesia research based on the idea that anesthesia and analgesia inhibit stress mechanism hyperactivity induced by surgery. The anesthesia research demonstrated that combinations of anesthesia and analgesia prevent stress and improve outcome better than either alone, but failed to clarify their confusing and overlapping effects or identify a practical method to optimize outcome, so that it too was abandoned. The habit of hyperventilation arguably caused this failure by rendering effective opioid analgesia dangerous. Nevertheless, the idea of a single physiologic mechanism that explains both tissue repair and hemodynamic physiology has never been disproved, and its theoretical potency remains undiminished.

Powerful new scientific theories often appear long before their time, and must await the death of critics and the accumulation of evidence before they gain acceptance. This appears to be the fate of Selye's ideas. In retrospect, the capillary gate and tissue repair theories formulated by the previous generation of stress researchers were amazingly insightful, but key evidence needed to show how these seemingly unrelated theories described semi-independent components of the same mechanism was lacking, so that it was impossible to identify a single mechanism that explained both tissue repair and hemodynamic physiology. However, since stress theory was abandoned more than 30 years ago, unrelated research has produced fresh evidence that has belatedly enabled the first crude description of the long-sought stress mechanism. It is called the "Stress Repair Mechanism" (SRM) [20]. The SRM is testable, and it fulfills all the predictions and expectations of stress theory. It enables Selye's Unified Theory of Medicine that confers cohesive explanations of embryological development, hemodynamic physiology, tissue repair, hemostasis, stress, anesthesia, analgesia, atherosclerosis, apoptosis, allostasis, amyloidosis, eclampsia, rheumatoid disease, infarction, essential hypertension, diabetes, eclampsia, malignancy, and

[1] Coleman, L. S., Intraoperative Hyperventilation May Contribute to Postop Opioid Hypersensitivity. *apsf Newsletter* March, 2010

more. This paper will focus on the intimately related new theories of anesthesia, analgesia, and allostasis.

A BRIEF OVERVIEW OF SRM OPERATION

A detailed and fully-referenced description of the SRM was recently published elsewhere [20]. The SRM is analogous to the older coagulation cascade concept, but it incorporates fresh evidence that enables it to explain embryological development, tissue repair, hemodynamic physiology, and hemostasis in detail, whereas the coagulation cascade provides only a partial explanation of coagulation.

The SRM (Fig. **1**) incorporates and explains both the venerable capillary gate and tissue repair theories that enabled its identification. The *capillary gate component* (CGC) corresponds to the intrinsic pathway of the coagulation cascade. It operates in flowing blood and regulates hemodynamic physiology, including blood viscosity and coagulability, capillary hemostasis, tissue perfusion, organ function, atherosclerosis, cardiac output, blood pressure, and heart rate. The *tissue repair component* (TRC) corresponds to the extrinsic pathway of the coagulation cascade. It continuously maintains and repairs extravascular tissues.

The vascular endothelium is the focus of SRM activity. It is a diaphanous layer of cells, one cell thick, that is the sole constituent of capillaries and covers the inner surface of larger blood vessels. It secretes tissue factor into extravascular tissues and isolates it from the enzymes in flowing blood. Tissue damage exposes tissue factor to Factor VII, which activates the tissue repair component.

The vascular endothelium also functions as an autonomic nervous gland that governs the capillary gate component. It releases von Willebrand Factor (VWF) into blood in accord with Sympathetic Nervous System (SNS) activity. It releases nitric oxide into blood in accord with Parasympathetic Nervous System (PNS) activity. VWF increases Factor VIII activity, which generates insoluble fibrin. Nitric oxide accelerates the spontaneous disintegration of insoluble fibrin. Autonomic balance thus governs the generation and disintegration of insoluble fibrin in capillaries and flowing blood, which explains capillary gate component activity. The vascular endothelium also produces several other hormones that regulate various aspects of SRM function, including Tissue Factor Pathway Inhibitor (TFPI), stoichiometric ATIII, Tissue Plasminogen Activator (TPA), and Protein C.

The tissue repair component and the capillary gate component share the blood-borne enzymatic interaction of hepatic Factors VII, VIII, IX, and X that generates *thrombin*, *soluble fibrin*, and *insoluble fibrin*. The combined effects of these three products explain all SRM manifestations. The capillary gate component controls Factor VIII. The tissue repair component controls Factor VII. Factors IX and X are produced continuously and do not fluctuate, so that the semi-independent activities of the capillary gate component and the tissue repair component govern the enzymatic interaction and the generation of its three products.

Thrombin is the "universal enzyme of extracellular energy transformation." It utilizes ATP to energize cell and enzyme activities including inflammation, immune activity, angiogenesis, mitosis, metabolism, chemotaxis, chemokine and cytokine release for cell communications, and the conversion of fibrinogen to soluble and insoluble fibrin. The SRM continuously governs thrombin generation in all tissues throughout the body to energize and regulate tissue maintenance and repair. Excessive thrombin causes harmful inflammation, cell hyperactivity, and malignancy. Apoptosis ensues when thrombin levels decline below a critical threshold.

Soluble fibrin is the "universal protein of tissue repair." Thrombin converts fibrinogen to fibrillar soluble fibrin that escapes from the vascular system *via* inflamed capillary walls and enters damaged tissues, where it supports the tissue repair process. It is the substance of pus, mucus, exudates, scabs, and collagen [21]. Excessive soluble fibrin production causes tissue edema and disrupts organ function. For example, it disrupts pulmonary gas exchange in pneumonia and placental function in eclampsia.

Insoluble fibrin is the "universal polymer of hemostasis." Factor VIII accelerates thrombin generation to energize its conversion of Factor X to Factor XIII, which adds molecular "cross-links" of fibronectin and plasminogen to fibrillar strands of soluble fibrin to generate three-dimensional insoluble fibrin that cannot escape the intact vasculature. Insoluble fibrin polymerizes into strands that bind to red cells. It spontaneously disintegrates into inert fibrin split products unless it is continuously stabilized by TAFI (Thrombin-Activated Fibrinolysis Inhibitor). Its disintegration is accelerated by nitric oxide (NO). Insoluble fibrin binds to red cells to halt capillary flow. It binds to red cells in flowing blood to increase turbulent flow resistance and inhibit turbulent mixing. When turbulent mixing declines below a critical threshold, insoluble fibrin binds red cells into a viscoelastic clot that regulates tissue repair. Insoluble fibrin effects thus explain coagulation, capillary hemostasis, blood viscosity, blood coagulability, organ regulation, atherosclerosis, tissue perfusion, organ function, infarction, glucose uptake, pulmonary embolus, tissue repair, and Disseminated Intravascular Coagulation (DIC).

THE CAPILLARY GATE COMPONENT

The capillary gate component simultaneously governs the generation and disintegration of insoluble fibrin to regulate a *capillary gate mechanism* in capillaries and a *turbulence mechanism* in arteries. These two mechanisms function differently but they act in concert to regulate blood flow in organs and tissues in accord with autonomic balance.

SNS activity "closes" the capillary gate component. It releases VWF from the vascular endothelium, which increases Factor VIII activity; generates insoluble fibrin in capillaries and flowing blood; alters arterial turbulence to increase blood viscosity and blood coagulability and accelerate atherosclerosis; activates capillary hemostasis; decreases cardiac output, cardiac efficiency, tissue perfusion, and organ function; and increases blood pressure and heart rate.

PNS activity "opens" the capillary gate component. It releases gaseous nitric oxide from the vascular endothelium

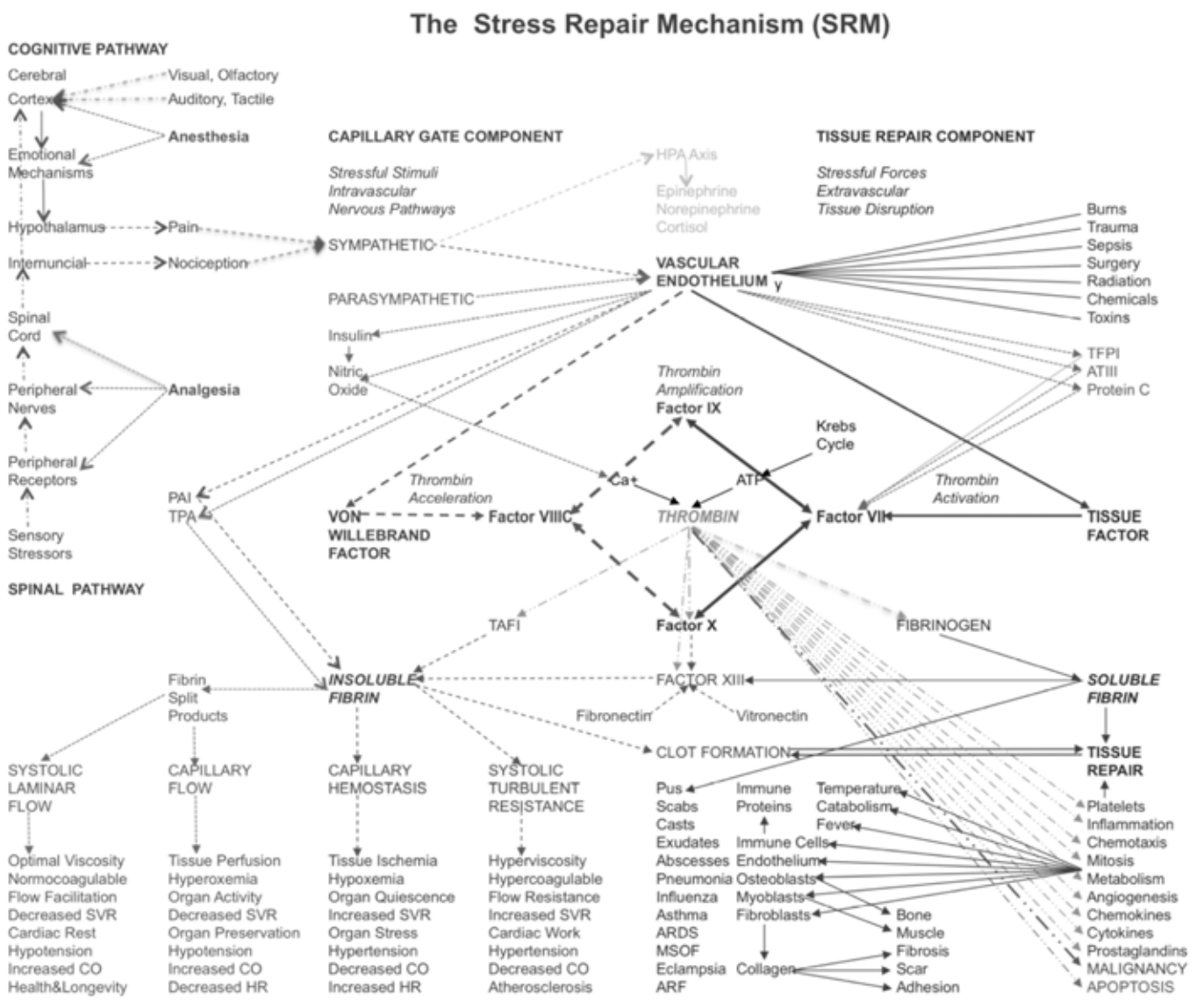

Fig. (1). The Stress Repair Mechanism (SRM) The SRM appears complex, but its underlying structure is simple and symmetrical. Arrows represent the influence (direct and indirect) that one biological function or reaction brings to bear on another. The SRM is analogous to the older "coagulation cascade" concept, but it combines more recent research information with capillary gate theory and tissue repair theory to produce a cohesive explanation of capillary hemostasis, tissue repair, physiology, and pathology as well as coagulation. The capillary gate component, shown in red (dashed lines), corresponds to the intrinsic pathway of the coagulation cascade. The tissue repair component, shown in blue (solid lines), corresponds to the extrinsic pathway of the coagulation cascade. Both the SRM and the coagulation cascade generate thrombin (orange, double-dashed lines), and convert fibrinogen to soluble fibrin and thence to insoluble fibrin. Inhibitory pathways appear in green (dotted lines).

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

that diffuses into blood. NO binds to Ca+ to inactivate thrombin, and thereby simultaneously inhibits insoluble fibrin generation and accelerates its disintegration. This reduces blood viscosity, increases cardiac output, reduces blood pressure and heart rate, reverses capillary hemostasis, enhances tissue perfusion, and promotes organ function.

The *capillary gate mechanism* regulates capillary flow, tissue perfusion, and organ function; it explains capillary hemostasis, infarction, and glucose uptake. SNS activity generates insoluble fibrin that binds to red cells to halt capillary flow. PNS activity disintegrates insoluble fibrin to restore capillary flow.

The *turbulence mechanism* is pertinent to anesthesia management, because it explains the hitherto mysterious nature of cardiac output, heart rate, blood pressure, Korotkoff sounds, bruits, the palpable pulse, atherosclerosis, blood viscosity, blood coagulability, and the hemodynamic effects of crystalloids, colloids, [22, 23] and blood transfusions. Red blood cells form "aggregate patterns" during systolic acceleration that eliminate 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. This explains why pulsatile blood flow operates at the threshold of maximum turbulence, and why atherosclerotic deposits form where turbulence is inadequate. Mammalian red cell morphology thus provides a combination of systolic flow efficiency that optimizes cardiac efficiency and exercise tolerance, and diastolic turbulent cleansing that minimizes atherosclerosis. This enhances cold tolerance compared to poikilothermic reptiles, but it necessitates increased food requirements to maintain body temperature above the threshold of lipoprotein solidification that increases blood viscosity [24].

The turbulence mechanism explains blood pressure. It is the lateral force generated by the diastolic wave of pulsatile blood turbulence as it travels proximal to distal with each heartbeat. Cuff inflation constricts arterial diameter, accelerates blood flow, and elevates turbulent frequencies to audible levels at the distal edge of the cuff to produce *Korotkoff sounds* that enable blood pressure measurement [25].

The main variable that affects blood pressure is blood viscosity that fluctuates in accord with autonomic balance. Stress activates the SRM and elevates blood viscosity, which increases blood pressure and accelerates atherosclerosis by exaggerating turbulent lateral forces at the expense of turbulent mixing effects. Increased viscosity also reduces stroke volume, elevates heart rate *via* the Starling Mechanism, and decreases cardiac output and tissue perfusion. Stress reduction 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.

Turbulent relationships are exponential in nature, so that small changes can produce large differences [26]. 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. Blood pressure is strikingly similar among most mammalian species because cardiac power generation is proportional to body size and most other variables are nearly identical [27]. However, unexpected aberrations can occur if one or more of these variables exceed their normal ranges.

I hypothesize that 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.

Oil pipelines illustrate the relationship between turbulence and atherosclerosis. Oil pipeline velocity must be maintained at the threshold of maximum turbulence to mobilize deposits from the inner walls of the pipes lest corrosive deposits accumulate. Similarly, pulsatile blood flow operates at the threshold of peak diastolic turbulence to mobilize deposits on the inner walls of arteries that induce atherosclerosis[2].

THE TISSUE REPAIR COMPONENT

The tissue repair component maintains and repairs extravascular tissues. Stressful forces damage tissues, disrupt the vascular endothelium, and expose extravascular tissue factor to enzymatic Factor VII in flowing blood. Tissue Factor activates Factor VII, which interacts with Factors VIII, IX, and X to generate thrombin, soluble fibrin, and insoluble fibrin in the immediate vicinity of the damaged tissues. Thrombin activates platelets and energizes the conversion of fibrinogen to soluble and insoluble fibrin. Soluble fibrin enters damaged tissues and provides a structural matrix that facilitates repair cell activity. Insoluble fibrin increases blood viscosity, reduces turbulent mixing below a threshold, and binds red cells into a viscoelastic clot that isolates flowing blood from damaged tissue. The selectively permeable viscoelastic clot substitutes for the damaged vascular endothelium and regulates contact between blood enzymes and tissue factor in the damaged

[2] Chris Woodyard, P. D. a. B. H. BP spill highlights aging oil field's increasing problems USA Today [Online], 2006. http://www.usatoday.com/money/industries/energy/2006-08-14-bp-cover-usat_x.htm?POE=click-refer.

tissues beneath the clot surface. The clot thus governs thrombin generation that energizes the cell and enzyme activities that repair tissues. These include inflammation that loosens cell connections to enable chemotaxis; chemotaxis that attracts repair cells into the damaged tissues; mitosis and metabolism of fibroblasts, osteoblasts and myoblasts that replaces damaged tissues; immune activity that removes debris and fights infection; chemokine and cytokine release that enables cell communications; and angiogenesis that perfuses the healing tissues. As the repair process nears completion, the vascular endothelium is restored, and this returns thrombin generation to maintenance levels, which causes apoptosis that shrinks wound tissues and concludes the repair process.

ANESTHESIA, ANALGESIA, AND THE THREE PATHWAYS OF SRM ACTIVATION

Three independent pathways activate the SRM: the *spinal pathway*, the *cognitive pathway*, and the *tissue pathway*. The spinal and cognitive pathways activate the capillary gate component, which elevates Factor VIII activity. The tissue pathway activates the tissue repair component, which increases Factor VII activity. 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, but they enable the SRM to focus its powerful effects. Analgesia inhibits the spinal pathway, and anesthesia inhibits the cognitive pathway. At present, there is no 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 [28]. Spinal pathway activity is called *nociception*. Descending cortical pathways inhibit nociception, so that their absence exaggerates nociception [29]. 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 [30-36]. 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 (see "The Cognitive Pathway" below) 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 [29, 37][3].

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 [38-40].

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) [7, 31, 36, 39, 41-60].

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 [61-67].

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 AND ALLOSTASIS

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 [68-73]. The cognitive pathway also inhibits spinal pathway nociception *via* descending pathways from the brain to the spinal cord [29]. Conscious awareness interprets nociception as *pain* [68, 69, 74-77]. 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

[3] Wickipedia. Autonomic Dysreflexia & Hyperreflexia. http://www.apparelyzed.com/autonomic.html.

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 [78, 79][4]. 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 [80]. 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" [68, 69, 74, 81][5]. This activates capillary hemostasis, and, increases blood viscosity [82, 83], 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, hyperglycemia and 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 [84].

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 [85]. 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[6].

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 [75, 84, 86-88].
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 [75, 86-92].
3. Anesthesia increases surgical safety by abolishing consciousness, fear, apprehension, and pain, but it cannot prevent harmful spinal pathway nociception in clinically practical doses [8, 9, 30-35].
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 [70, 74, 84, 89, 93-101].
5. Chronic emotional allostatic load, such as job difficulties, elevates VWF and Factor VIII activity, accelerates atherosclerosis, and shortens life span [72, 73, 82, 102-104].
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 [88, 90-92].
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 [8, 105, 106].

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. 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) [107-113].
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 [114-116].
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

[4] Wickipedia. Hyperthymestic Syndrome. http://en.wikipedia.org/wiki/Hyperthymesia.
[5] Behar, M. Can Fear Be Forgotten *Popular Science* [Online], 2007. http://www.popsci.com/scitech/article/2007-12/can-fear-be-forgotten.
[6] Behar, M. Can Fear Be Forgotten *Popular Science* [Online], 2007. http://www.popsci.com/scitech/article/2007-12/can-fear-be-forgotten.

inflammatory changes that enable soluble fibrin to enter extravascular tissues, causing tissue edema and organ dysfunction [111, 117-122].

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 [123, 124].
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 [111].
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) [125-127].

FRESH DEFINITIONS ENABLED BY THE SRM

The inability to explain stress-related phenomena has caused their definitions to remain imprecise. 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"[7]. 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"[8]. 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 [29]. 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 complete 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 suppresses 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

[7] http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/HTMLDisplay.cfm&ContentID=1728

[8] http://www.stress.org/topic-definition-stress.htm?AIS=7cb3d72c6c85f49f51be5b1f3ee387cb

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.

POSITIVE FEEDBACK AND THE SRM

The capillary gate component regulates Factor VIII activity in accord with nervous stimuli, and the tissue repair component regulates Factor VII activity in accord with tissue disruption. Both components share the enzymatic interaction of Factors VII, VIII, IX, and X, so that the activity of each exaggerates that of the other. Their constantly fluctuating semi-independent activity explains the bewildering variety of SRM manifestations. The interaction of the two components induces positive feedback that produces rapid, powerful, focused responses to stressors to maintain and repair body tissues. If stressors subside, the subsequent tissue repair process invokes negative feedback that gradually restores SRM activity to maintenance levels. However, prolonged and exaggerated stressor activity causes positive feedback to overwhelm negative feedback, causing potentially lethal overproduction of thrombin, soluble fibrin, and insoluble fibrin. For example, infrarental aortic surgery impairs pulmonary function [128, 129]. SRM activity thus explains the complex relationships between and among surgery, diseases, stresses, and physiology as predicted by Selye. Control of the SRM confers benefit in numerous pathological conditions, including malignancy, eclampsia, pneumonia, asthma, influenza, sepsis, Multi-Organ Failure Syndrome (MOFS), and the Surgical Stress Syndrome.

ANESTHESIA, ANALGESIA, SURGICAL STRESS AND THE SRM

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 [124, 128-132]. This manifests as symptoms distant from the location and time of surgery [5, 128, 129, 133-138]. Anesthesia controls the cognitive pathway, and analgesia controls the spinal pathway, but no available treatment controls the tissue pathway. Either anesthesia or analgesia can independently reduce positive feedback and surgical stress to the point that most patients survive surgery [61-63, 139, 140], 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 [1, 7-9, 30, 32, 40, 61, 62, 66, 106, 141-163]. Such combinations beneficially minimize positive feedback [164]. They reduce blood viscosity and coagulability, improve tissue perfusion and oxygenation, protect organ function, maintain cardiac output, reduce blood pressure, increase ejection fraction, slow heart rate *via* the Starling Mechanism and minimize fever, tachycardia, hypertension, dysrhythmias, infarction, mental confusion, malignancy, heart disease, and other manifestations of positive feedback in the aftermath of surgery [5, 6, 9, 141, 142, 152, 156, 165-186].

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. Polypharmacy confers no benefit, and it increases toxicity and undermines predictability. Theoretically, the additional neutralization of tissue factor released into blood during surgery should abolish the Surgical Stress Syndrome altogether [36, 64, 107, 111, 121, 187].

HEMODYNAMIC PHYSIOLOGY AND PHARMACEUTICAL EFFECTS

Hemodynamic physiology is customarily explained by direct autonomic innervation that regulates cardiac inotropy and chronotropy and/or arteriolar contraction and relaxation. 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, sustained increases in cardiac work cause congestive heart failure, while 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 cause capillary proliferation that reduces vascular resistance and improves cardiac efficiency. The capillary gate component 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 blood pressure and the palpable pulse.

In 1965, Holemans reported that all “vasoactive” drugs increase fibrin turnover, and that “vasoconstrictors” cause greater fibrin turnover than “vasodilators.” His report generated considerable interest, but could not be appreciated without a logical explanation [188]. The capillary gate component explains Holemans’ observations. Fibrinolysis (i.e. the disintegration of insoluble fibrin) produces “Fibrin Split Products” (i.e. FSP, or “d-dimer”). “Vasodilator” drugs promote fibrinolysis that opens the capillary gate, reduces blood viscosity, lowers blood pressure, enhances perfusion, and releases FSP into blood. “Vasoconstrictor” drugs promote fibrinogenesis (i.e. insoluble fibrin generation) that closes the capillary gate, elevates blood viscosity, inhibits perfusion, and increases blood pressure. Fibrinogenic drugs ultimately cause greater fibrin turnover than fibrinolytic drugs, because they generate increased quantities of insoluble fibrin that subsequently disintegrate into FSP. The terms vasoconstrictor, vasoconstriction, vasodilator, vasodilation, and vasoactive are all misnomers. Drugs that affect blood viscosity are better described as “fibrinogenic” and “fibrinolytic.”

Parathyroid glands govern blood Ca+ levels within a narrow range to optimize thrombin activity that is essential for SRM activity [189]. Low Calcium levels inhibit thrombin, which impairs both the generation and stabilization of insoluble fibrin, and undermines hemostasis [189-192]. The blood preservatives Trisodium citrate and EDTA bind strongly to Ca+ and halt fibrinogenesis and clot formation. Their effects are reversed by Calcium [190]. Calcium chloride and calcium gluconate elevate serum Ca+ levels, increase thrombin activity, promote fibrinogenesis, close the capillary gate, and cause sharp, short-lived increases in blood viscosity that increase BP and reduce cardiac index [193].

Nitroprusside (NTP) and nitroglycerine (NTG) exert their fibrinolytic effects by releasing nitric oxide from the vascular endothelium that binds to Ca+ and reduces thrombin activity [194, 195].

MgSO4 competitively inhibits ca+, retards fibrino-genesis, promotes fibrinolysis[196-199] prevents stent thrombosis [200], mitigates myocardial infarction mortality [201, 202], inhibits blood hypercoagulability caused by crystalloids [23], and moderates eclampsia [203].

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+.[204-217] A fibrinolytic effect that reduces both pulmonary and systemic vascular resistance and improves cardiac efficiency and organ perfusion is the simplest explanation for the benefits of these drugs [218]. These drugs also inhibit platelet activity, promote bleeding, and improve pulmonary hypertension (especially when combined with "anticoagulant" medications), all of which is explained by their ability to inhibit thrombin [191, 192, 211, 217, 219, 220].

Vasopressin promotes beneficial fibrinolysis by activating plasmin [130].

Epinephrine releases VWF from the vascular endothelium to induce capillary fibrinogenesis and capillary gate closure, and this explains how it increases systemic vascular resistance and blood pressure [209]. Astrocytes protect brain perfusion from epinephrine effects, which explains why the use of epinephrine during cardiac arrest does not cause brain damage [221, 222].

Salicylates exert their anti-inflammatory and anti-platelet effects by interfering with thrombin [223]. Glucocorticoids inhibit the cellular effects of thrombin [224]. Anticoagulant medications have no direct effect on vascular smooth muscle, but they interfere with thrombin production and fibrinogenesis, and this explains how they retard athero-sclerosis, mitigate hypertension, and prevent sickle cell anemia crisis [217, 225, 226].

Lidocaine, prilocaine, and marcaine are traditionally called "local anesthetics" because of the misconception that anesthetics have analgesic properties, but they are more logically called "local analgesics" because they inhibit nociception. They block the function of exposed Sympathetic nerve endings that directly activate the vascular endothelium in addition to their ability to block nerve conduction [227, 228]. They prevent the release of VWF from the vascular endothelium, and inhibit the capillary gate component [28, 141, 227, 229-236]. Local analgesics increase capillary flow and reduce coagulability and surgical stress whether administered *via* intravenous, tissue infiltration, epidural or spinal routes [28, 44, 46-49, 141, 169, 173, 227, 229, 232, 233, 237-239]. When administered intravenously they reduce blood coagulability, bronchial hyper-reactivity and surgical stress [28, 35, 235, 240-242]. When infiltrated into tissues they increase capillary flow and inhibit capillary hemostasis [227, 237, 239].

Sildinafil mimics PNS 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, and achalasia as well as erectile dysfunction [243-265].

The ability of Angiotensin Converting Enzyme (ACE) inhibitors to control hypertension is presently attributed to their effects on angiotensin, but is better explained by their reduction of VWF levels [266]. VWF functions as a structural component of the capillary gate mechanism, which explains why VWF damage or depletion causes angioneurotic edema and angiodysplasia [20]. The reduction of VWF explains how ACE inhibitors reduce systemic vascular resistance and increase cardiac output, and why they cause unpredictable tissue edema and swelling that is analogous to angioneurotic edema. They are contra-indicated in patients with aortic valve replacements and aortic outflow obstruction, because these conditions cause increased blood turbulence that physically damages VWF molecules, which are large and fragile [267-271].

DIC, ECLAMPSIA, IV FLUID AND BLOOD THERAPY, AND THE SRM

Disseminated Intravascular Coagulation (DIC) is also known as "consumptive coagulopathy," because it involves abnormal systemic intravascular coagulation that consumes and depletes coagulation enzymes and precursors and causes systemic bleeding. It is caused by the abnormal entry of tissue factor into systemic blood circulation. This activates Factor VII, overwhelms inhibitory mechanisms, and initiates excessive intravascular generation of thrombin, soluble fibrin, and insoluble fibrin. Insoluble fibrin reduces blood turbulence below a threshold, whereupon spontaneous systemic coagulation begins [272, 273]. This depletes coagulation enzymes and precursors and distorts the coagulation process. Thrombin converts fibrinogen to soluble fibrin, which depletes fibrinogen [124, 274-276]. Exaggerated Factor VIII activity converts Factor X to Factor XIII to convert soluble fibrin to insoluble fibrin, but this depletes Factor VIII [277, 278]. Factor XIII adds "cross-links" of fibronectin and plasminogen to soluble fibrin to generate insoluble fibrin, and this consumes both Factor XIII and fibronectin [278-281]. Shortages of Factor XIII and fibronectin cause soluble fibrin to accumulate to excessive blood levels [275, 276]. Fibronectin exhaustion also causes Factor XIII to produce defective forms of insoluble fibrin

with inadequate fibronectin "cross-links." This causes defective clot formation [282]. These imbalances cause soluble fibrin to form abnormal attachments to the pathological clots to produce "microthrombi." Soluble fibrin also deposits on arterial walls [283]. These phenomena characterize DIC [284-286]. The abnormal coagulation activity reduces circulating red cell mass, which exaggerates blood turbulence and further inhibits effective coagulation. Continuing loss of red cell mass due to bleeding aggravates the problem.

DIC most often occurs in patients who undergo extensive surgical intervention in the immediate aftermath of major trauma and massive blood loss [287-289]. Trauma and surgery both release tissue factor into systemic circulation and increases Factor VII activity, causing SRM hyperactivity and positive feedback [273, 290, 291]. In addition, trauma patients are typically subjected to starvation, sepsis, hypothermia, emotional stress, physical pain, hypoxia, and iatrogenic hyperoxia, and these additional forms of stress exaggerate positive feedback [101, 231, 278, 287, 289, 292-296].

Normal pregnancy is a stressful condition characterized by elevated blood levels of Factor VIII and insoluble fibrin that increase blood viscosity and coagulability [297]. Stressful conditions such as diabetes, obesity, and sepsis (commonly caused by occult urinary tract infections during pregnancy) can increase the risk of eclampsia by increasing SRM activity above the level of normal pregnancy [278, 297-302]. 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 [124-127, 230, 273, 303]. 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 [126, 127, 273, 274].

Several factors can confuse and aggravate DIC. Crystalloids, colloids, and starch solutions can alter blood turbulence and dilute coagulation precursors and enzymes [22, 23]. DIC removes red cells from circulation, causing anemia that exaggerates blood turbulence and inhibits coagulation [304]. Blood transfusion corrects the anemia, reduces blood turbulence, and increases blood coagulability, but excessive transfusion with washed, packed red cells devoid of plasma can 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 [292]. Severe hypothermia impairs SRM enzymes, and inhibits hemostasis [288]. Metabolic acidosis and hypothermia synergistically impair hemostasis [305].

BLOOD PRESSURE AND ANESTHESIA MANAGEMENT

Blood pressure is a confusing, counterintuitive, and potentially counterproductive standard of anesthesia monitoring. It 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.

During anesthetic induction, hypnosis 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 and increased blood viscosity 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 causes problematic muscle tension and unexpected movements. Anesthesia does not prevent these problems. Muscle relaxants control the symptoms of wind up syndrome, but do not inhibit the occult nociception that is the cause. The occult spinal pathway activation continues to affect spinal cord activity, causing the release of stress hormones and elevating 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 [8, 106]. 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 [128, 129]. 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. However, there is no presently available means to inhibit the tissue repair component, so surgical stress cannot be completely abolished.

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 [22, 23].

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, inhibits atherosclerosis, and minimizes positive feedback that causes malignancy and heart disease in the distant aftermath of surgery.

CONCLUSION

The Unified Theory of Medicine postulated by Hans Selye promises to elevate medicine from an art based on experiment to a science founded on theory. The SRM provides the long-sought means to test this theory. Anesthesiologists are poised to confirm the SRM using conventional anesthesia techniques. Pharmaceutical research can then develop safe ways to neutralize tissue factor in blood circulation and eliminate the Surgical Stress Syndrome altogether. This will enable a new era of surgical progress. The SRM promises to inspire and guide efficient pharmaceutical research to produce effective treatments for epidemics, malignancy, rheumatoid disease, eclampsia, atherosclerosis, amyloidosis, pneumonia, asthma, sepsis, and other presently mysterious conditions, and introduce a new era of health, longevity, and productivity.

ABBREVIATIONS

SRM	=	Stress Repair Mechanism
TRC	=	Tissue Repair Component
CGC	=	Capillary Gate Component
SSS	=	Surgical Stress Syndrome
vWF	=	von Willebrand Factor
SNS	=	Sympathetic Nervous System
PNS	=	Parasympathetic Nervous System
NO	=	Nitric Oxide
ATP	=	Adenosine Tri Phosphate
CO2	=	Carbon Dioxide
FICO2	=	Fraction Inspired Carbon Dioxide
TFPI	=	Tissue Factor Pathway Inhibitor
HPA	=	Hypo Pituitary Adrenal Axis
DIC	=	Disseminated Intravascular Coagulation
NSAID	=	Non-Steroidal Anti-Inflammatory Drug
MOFS	=	Multi-Organ Failure Syndrome
EDTA	=	Ethylene Diamene Tri-acetic Acid
NTP	=	Nitroprusside
NTG	=	Nitroglycerine
MgSO4	=	Magnesium Sulphate
ACE	=	Angiotensin Converting Enzyme
HAPE	=	High Altitude Pulmonary Edema

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