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Review

## The Initial Common Pathway of Inflammation, Disease, and Sudden Death

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**Abstract:** In reviewing the literature pertaining to interfacial water, colloidal stability, and cell membrane function, we are led to propose that a cascade of events that begins with acute exogenous surfactant-induced interfacial water stress can explain the etiology of sudden death syndrome (SDS), as well as many other diseases associated with modern times. A systemic lowering of serum zeta potential mediated by exogenous cationic surfactant administration is the common underlying pathophysiology. The cascade leads to subsequent inflammation, serum sickness, thrombohemorrhagic phenomena, colloidal instability, and ultimately even death. We propose that a sufficient precondition for sudden death is lowered bioavailability of certain endogenous sterol sulfates, sulfated glycolipids, and sulfated glycosaminoglycans, which are essential in maintaining biological equipose, energy metabolism, membrane function, and thermodynamic stability in living organisms. Our literature review provides the basis for the presentation of a novel hypothesis as to the origin of endogenous bio-sulfates which involves energy transduction from sunlight. Our hypothesis is amply supported by a growing body of data showing that parenteral administration of substances that lower serum zeta potential results in kosmotropic cationic and/or chaotropic anionic interfacial water stress, and the resulting cascade.

**Keywords:** inflammation; serum sickness; colloidal instability; interfacial water stress; bio-sulfates; Shwartzman phenomena; sudden death syndrome

PACS Codes: 87.15, 87.19, 87.19.ly, 87.50.cf

## Glossary of Terms

<b>Anaphylaxis</b>	a severe, rapidly progressing, life-threatening, generalized allergic reaction.
<b>Biological equipoise</b>	a stable, non-equilibrium, dissipative system synonymous with life.
<b>Cholesterol sulfate (Ch-S)</b>	quantitatively the most important known sterol sulfate in human plasma where it regulates the activity of the serine proteases, in cell membranes where it has a stabilizing role, and in platelet membranes where it supports platelet adhesion.
<b>Coherence domain (CD)</b>	a water CD is a collection of liquid water molecules which oscillate in unison in tune with a self-trapped electromagnetic field at a well-defined frequency. The coherent oscillations produce an ensemble of quasi-free electrons, able to collect noise energy from the environment and transform it into high-grade coherent energy in the form of electron vortices. This high-grade energy may then activate biomolecules resonating with the water CD.
<b>Colloidal instability</b>	a property attributed to a colloidal suspension that develops when stabilizing repulsive steric and electrostatic forces between colliding particles are insufficient to prevent their natural tendency to aggregate into masses large enough to precipitate.
<b>Colloidal suspension</b>	a colloid that has a continuous liquid phase in which a solid is suspended in a liquid, e.g., our flowing blood.
<b>Exclusion zone (EZ)</b>	a glass-like, gel phase consisting of water CDs resonating in-phase, adjacent to hydrophilic surfaces, several hundred micrometers wide which excludes colloidal particles and various solutes as a consequence of water molecules re-orienting to produce a more ordered structure, which then excludes the particles.
<b>Exogenous interfacial water stress (EIWS)</b>	a property of interfacial water—interfacial tension—which destabilizes enzymes, protein structure, and cell membranes.
<b>Glycosaminoglycans</b>	a group of high molecular weight linear polysaccharides constructed with various disaccharide repeating units usually occurring in proteoglycans, including the chondroitin sulfates, dermatan sulfates, heparan sulfate and heparin, keratan sulfates, and hyaluronic acid, with the primary configurations containing an amino sugar and a uronic acid.
<b>Hofmeister series</b>	the Hofmeister series or lyotropic series is a classification of ions in order of their ability to change water structure. A scale can be established wherein: <b>kosmotropic</b> ions or nonionic kosmotropes stabilize proteins and hydrophobic aggregates in solution and reduce the solubility of hydrophobes, and <b>chaotropic</b> ions or nonionic chaotropes unfold proteins, destabilize hydrophobic aggregates and increase the solubility of hydrophobes.

<b>Interfacial tension</b>	a measure of the cohesive (excess) energy present at an interface arising from the imbalance of forces between molecules at an interface (gas/liquid, liquid/liquid, gas/solid, liquid/solid). The excess energy is called surface free energy and can be quantified as a measurement of energy/area, <i>i.e.</i> , the energy required to increase the surface area of the interface by a unit amount.
<b>Jones-Ray effect</b>	the observation of a minimum in the surface tension at very low ionic concentrations (<1 mM).
<b>Kinetic Terahertz Absorption (KITA)</b>	KITA monitors the changing THz electric field pulse shape on the picosecond time scale $\Delta t$ , as a chemical reaction proceeds on a longer time scale $t$ , and has been applied to measure the changing protein-hydration-water dynamics.
<b>Shwartzman reaction</b>	or Shwartzman phenomenon occurs when a “preparatory”, <i>i.e.</i> , injection of bacterial filtrates, is followed after a proper time interval by intravenous “provocation” with the same or some similar material.
<b>Surface tension</b>	the cohesive forces among liquid molecules responsible for the surface free energy at a gas liquid interface is produced by the attraction between the molecules being directed away from the surface as surface molecules are more attracted to the molecules within the liquid than they are to molecules of the gas at the surface.
<b>Surfactant</b>	in principle, anything can be called a surfactant that affects the surface tension of a liquid, the interfacial tension between two liquids, or that between a liquid and a solid.
<b>Thrombohemorrhagic phenomenon (THP)</b>	a change characterized by thrombosis and hemorrhage.
<b>Zeta potential (ZP)</b>	a measure of the net charge density of a particle.

## 1. Introduction

An extensive review of the colloid and interface science literature has led us to conclude that the very earliest events in inflammation, disease, and sudden death are purely biophysical. We now strongly believe that biophysical properties underlie the origin, development, and perpetuation of life. The evidence also supports our view that inflammation, disease, and sudden death rest on purely biophysical events that provoke a branching, cascade-like, chain of reactions, which typically begins in our vascular system. The literature amply supports the concept that our vascular system, including the molecular and humoral immune defense and lymphatic systems, acts as though it is a single organ [1]. Both microvascular disease and endothelial dysfunction share a common initial pathophysiology. A better understanding of these earliest of biophysical events will enable a more rational approach to dealing with many of today’s idiopathic diseases. These diseases, are likely to be pluricausal [2] and highly stereotyped [3] in their clinical presentations, often with substantial overlap of symptoms.

In this review, we hope to highlight, summarize, and call attention to some of the many historical milestones we have relied on to recommend areas of further research in the diagnosis, treatment, and prevention of disease. We believe that the development of sustainable health paradigms of *tomorrow* will require a multidisciplinary approach *today*. This approach will, at times, require each of us to look to the literature found in diverse fields of endeavor, for better understanding, particularly in areas in

which we were not formally trained. We have purposefully chosen to limit the scope of this review to simply trying to prospectively identify, at least in broad terms, potentially fruitful areas of future research which might have meaningful impact on the public health. The references cited in support of this review are intended to give the reader a place to begin. Lead references are cited upon which to base further inquiry.

We will begin this review by discussing the definition and clinical characteristics of a syndrome of events, the net outcome of which is all too often, the sudden death of the victim. We will follow with a delineation of some of the underlying colloid and interface science which can reasonably be implicated in the pathophysiology of sudden death. We will present the preclinical research which we believe is most relevant to understanding sudden death. We will give examples of ongoing clinical research which are the progeny of colloid and interface science. We will present a novel hypothesis as to the origin of endogenous bio-sulfates, and discuss their central role in the establishment and maintenance of our biomembranes. We focus on the glycocalyx layers upon which rests the interfacial stability and function of our biomembranes in health. We will detail the role of the nitric oxide synthase family of enzymes, which, we argue, plays an essential role in energy capture and energy transduction, in support of the integrity of our biomembranes. We will introduce and define the concept of exogenous interfacial water stress (EIWS) and review several clinically-relevant sources of EIWS. Throughout this review we will endeavor to point out the necessary, central role of interfacial water as an essential reactant, mediator, and effector molecule in our bodies. Since water is the most abundant molecule on Earth and in our bodies, and the third most abundant molecule in the Universe (after H and CO), and because the vast majority of water in our bodies is interfacial water, it is in no way unreasonable to conclude that life without water is an impossibility.

In the recent medical literature, SDS (Sudden Death Syndrome) is used as an umbrella term for a number of conditions that can lead to a sudden death. Two distinct forms of SDS have been identified: Sudden *Infant* Death Syndrome (SIDS) and Sudden *Adult* Death Syndrome (SADS). In this paper, we expressly define Sudden Adult Death Syndrome (SADS) as non-traumatic, non-violent, and unexpected occurrences resulting from unknown cause. We strongly believe that defining SADS as Sudden Arrhythmia Death Syndrome or as Sudden Cardiac Death is misleading and unfortunate because such a definition (a) infers a cardiac etiology, when the etiology is often unknown; (b) infers a six hour or less time frame, when the time frame is also unknown; and (c) limits by inference any open-minded investigation as to the actual cause to solely cardiac etiologies, when other etiologies may well exist.

Multiple hypotheses have been proposed as the pathophysiologic mechanisms responsible for SIDS. However, none have been proven. The triple-risk model of SIDS proposes that the cause of SIDS is multifactorial, and that the sudden death of an infant may occur when a predisposed infant in an unstable period of homeostatic control is exposed to triggering factors [4]. Examples of various proposed etiologies include the QT interval hypothesis, the apnea hypothesis, neuroconvulsive, anaphylactic, thrombohemorrhagic, infectious, inflammatory, genetic, e.g., Brugada's syndrome [5], and brainstem etiologies [6]. SIDS is a diagnosis of exclusion used to describe the sudden and unexpected death of an infant when no other plausible cause can be found [7]. Factors such as maternal smoking, prone sleeping, infection, lack of breast feeding and overheating have all been associated

with SIDS mortality [8]. Several theories have been proposed to explain the sudden deaths in this age group; however, the mechanisms responsible for SIDS remain poorly understood [6,9–15].

Colloid and interface science literature supports the novel view that all instances of SDS share an *initial* common pathophysiology which is purely biophysical. Hofmeister (1888) ordered anions according to their ability to precipitate globular proteins from water [16]. Setschenow (1889) established an empirical law linking the solubility of a protein with cosolute (salt) concentration [17]. Heydweiller (1910) discovered that salt dissolved in water increased the surface tension of the solution-air interface [18]. Langmuir (1917) was the first to attempt a theoretical explanation of the physical mechanism behind the increase in surface tension produced by electrolytes [19]. More recently, Dér *et al.* instead of focusing on air-water surface tension, used protein-water interfacial tension as a general description of the free energy changes associated with salt-induced changes of protein solubility and conformation [20,21]. In general terms, the interfacial tension is determined by the cohesion and adhesion free energies within and between phases separated by the interface, respectively. Fluctuations in protein conformation are linked to interfacial tension and protein structural stability [22–25]. The fluctuation-dissipation theorem [22] was first proven by Callen and Welton in 1951. This theorem describes how dissipative forces and fluctuating random forces are connected. According to Grassia in 2000, when a large particle moves through a sea of small particles, on the microscale, all particle collisions are elastic. However, on the macroscale, where only the large particle is properly resolved, dissipative forces and fluctuating random forces are observed [23]. Many working proteins (functional proteins such as enzymes) oscillate between “open” and “closed” conformations, which also implies water-exposed surface area changes [20,21]. Hofmeister ion-dependent fluctuations at the interface are implied. Hofmeister effects can be rationalized by considering the contribution of interfacial energy to the total free energy change of the protein. A general relationship exists between salt concentration and protein-water interfacial tension. Protein-water interfacial tension plays a key role in protein structure and dynamics. An essential role for correct protein folding can be gleaned from the observation that the unfolded protein response is a common stressor leading to cellular apoptosis.

Rosina has reported the temperature dependence of blood surface tension of healthy subjects [26]. There is now ample literature [27–39] to support the conclusion that many of the surfactants, administered parenterally to humans in vaccines, such as aluminum, mercury, and polysorbate 80 (in the acidic pH range), raise blood surface tension, leading to an increase in surface tension of intracellular, extracellular, and interstitial water, resulting in a pathology that we will refer to henceforth as “water stress”. Throughout this paper, we will refer to water stress as a property of interfacial water—interfacial tension—which destabilizes enzymes, protein structure, and cell membranes [20,21,40–49].

Several compelling examples of water stress as applied to humans can now be cited [26,37,38,44,45,47–57]. Polycation-induced agglutination and sensitization of red blood cells has been demonstrated by several investigators [47–49,58–67]. In 1985, Coakley *et al.* demonstrated a regular periodicity of cell-cell contact points by both light microscopy and transmission electron micrography of polylysine agglutinated erythrocytes [44,49,68–70]. Serum surface tension was reported by Enoki Yoshisuke to be transiently elevated after provocation injection for the Shwartzman reaction [71]. Absolom has data showing that the surface tension of erythrocytes obtained from untreated cardiac arrhythmia patients

was higher than that of treated patients [45]. Kratochvil and Hrnčir demonstrated that the level of surface tension of the blood marks changes occurring in various disease conditions such as rheumatoid arthritis, proliferative glomerulonephritis, and some tumors of the central nervous system or the urogenital tracts [72]. Kazakov *et al.* applied dynamic surface tensiometry of serum and cerebrospinal fluid for diagnosis and monitoring of treatment in patients with rheumatic, neurological and oncological diseases [57]. Esitashvili and Msuknishvili observed an increase in blood surface tension during acute myocardial infarction in humans [54]. Electrostatic interactions and interfacial charge regulation of biomembranes is a focus of intense ongoing research [65–67,73–81]. Fiszer-Kierzkowska recently suggested that cationic liposomes may not be suitable vehicles for gene transfection, given that they produced apoptosis and aggregation of misfolded proteins and/or fluidity changes of cellular membranes [82].

Recently, experiments with yeast and in cardiac cells by Lloyd *et al.* has revealed astonishing parallels and similarities in their dynamic biochemical organization, despite being separated by 1.2 billion years of evolution according to the prevailing orthodoxy [83]. This is not the first time that oscillatory fluctuations of characteristic periodicity have been noted in living tissue. Fluctuating phenomena of this nature have been studied for almost a decade. They are likely to be mesoscopic, supramolecular manifestations of the fluctuation-dissipation theorem [22].

Literature review provides strong support for our conclusion that the serial parenteral administration of both polycationic and non-ionic surfactants is causing cumulative, synergistic, and systemic interfacial water stress. Non-ionic surfactants, e.g., Triton 100 and Tween 80, found in many of today's marketed vaccines, can induce apoptotic cell death [36,84], hemolysis [32,33,38], and meningoencephalitis [85]. Aluminum hydroxide gels have been used as vaccine adjuvants for many years. There is a well-known relationship between hemolytic activity and adsorption capacity of aluminum hydroxide adjuvants [28]. Intraperitoneal exposure to aluminum sulfate in rats increases blood viscosity and red blood cell aggregation [86]. A link between aluminum and the pathogenesis of Alzheimer's disease was recently proposed [87]. Aluminum hydroxide injections have been shown to lead to motor deficits and motor neuron degeneration in mice [88]. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex. Morin stain detected the presence of aluminum in the cytoplasm of motor neurons with some neurons also testing positive for the presence of hyper-phosphorylated tau protein, a pathological hallmark of various neurological diseases, including Alzheimer's disease and frontotemporal dementia. Aluminum (Al), the most commonly used vaccine adjuvant, is a demonstrated neurotoxin and a strong immune stimulator. Hence, adjuvant Al has the potential to induce neuroimmune disorders. Al in vaccines may also be a contributing factor in autism spectrum disorder (ASD) [89–93].

More than a century ago, in 1858, the Russian investigator Botkin first described what later became known as “erythrocyte agglutination thrombi” [94]. In 1894, Sanarelli first observed a condition which later became known as the generalized Sanarelli-Schwartzman phenomenon (SSP-G) [95], after further clarification by Schwartzman in 1928 [3,96]. There is ample evidence in the literature that this is an appropriate model for serial exogenous surfactant administration, as in scheduled vaccination programs, and it may constitute a “preparatory” or “sensitizing” or “priming” event. A final “provocation” or “challenge” or “shocking” event may induce a chain of reactions or a branching (avalanche-like)

cascade of events [97–102], equated with the Sanarelli-Shwartzman Phenomenon, whether localized or generalized [3,97,98,103,104].

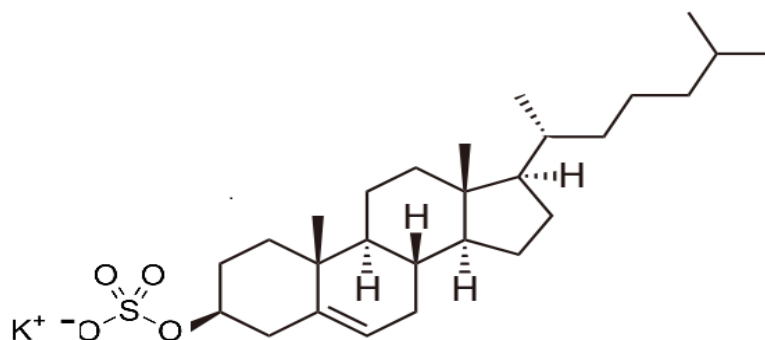
Thrombohemorrhagic phenomena (THP), also either localized (THP-L) or generalized (THP-G), are manifestations of the nonspecific or generalized stress adaptation syndrome [105]. In 1981, there was a proposal for a univisceral or single organ third type of Shwartzman reaction [106]. Sometimes, after the inflammatory cascade is “induced”, a new equilibrium is achieved, albeit in a more susceptible state for further subsequent thrombohemorrhagic events, which are sometimes fatal, depending critically upon such factors as the blood  $\zeta$ -potential (zeta potential, to be abbreviated herein as ZP) and surface tension, in part controlled by bio-sulfate levels. Whether this is truly a “new equilibrium” or a “stable, non-equilibrium” or an “unstable, non-equilibrium” is uncertain to the authors, in light of Bauer, Voeikov and Del Giudice, and Morowitz and Smith [101,102,107]. Our literature review supports the view that human blood ZP, serum surface tension, and systemic bio-sulfate levels [76,108–113] should be employed clinically as biomarkers for risk of SDS. Such biomarkers might thereby guide future preventive health strategies.

In this paper, we introduce a novel hypothesis to explain sudden death, relating impaired sulfur metabolism to serum colloidal instability. We argue that individuals with such impairment are vulnerable to an acute reaction to exposure to toxins that would otherwise be efficiently expelled from the body. Cholesterol sulfate (Ch-S), whose structure is depicted in Figure 1, sulfated glycosaminoglycans (sGAGs), and sulfated glycolipids play an essential role in maintaining the *in vivo* serum ZP in all living organisms. Any process which acutely lowers the ZP, such as the introduction of polycationic surfactant stress into the vascular system, has the potential to trigger SDS. Mediated by water, this manifests hemodynamically as increased viscosity, decreased RBC and vascular distensibility, increased vascular permeability, acutely deranged ionic gradients [ion channelopathy], colloidal instability, abnormal blood flow dynamics, impaired tissue oxygenation and oxygen delivery, thrombohemorrhagic phenomena, microvascular ischemia, cellular anoxia, infarctions, cell necrosis, and death.

While we believe that everyone is vulnerable to SDS, some are more vulnerable than others. A child’s prenatal (via the mother) and postnatal nutritional status are important determinants of risk [114]. Adequate blood Ch-S sources are essential to health, e.g., adequate endogenous and exogenous cholesterol [114–117] and sulfur [114,118], as well as certain minerals and cofactors, e.g., zinc and tetrahydrobiopterin (BH<sub>4</sub>). Sunlight exposure to the skin is essential in the production of Ch-S (as well as its derivative, vitamin D<sub>3</sub>-sulfate), and excessive use of sun block will interfere with this process [114]. We propose that lowered levels of endogenous sterol sulfates, sulfated glycolipids, and sulfated GAGs are a sufficient risk factor for sudden death, in the context of cationic surfactant water stress. These biologically active molecules are essential for maintaining biological equipose, energy metabolism, membrane function, and thermodynamic stability in living organisms.



Figure 1. Cholesterol sulfate.



This review calls attention to the very earliest perturbations to our living internal biological milieu that we believe are common to all pathways to the sudden death syndrome. These involve cationic kosmotropic or anionic chaotropic surfactant induction of interfacial water stress, lowering of ZP, colloidal instability, membrane instability, cellular dysfunction, and electrokinetic, hemorrheologic, and hemodynamic derangements. We propose that the induction of interfacial water stress is mediated by exogenous dietary and environmental exposures, often in the form of polycationic surfactants, some of which are parenterally administered, hence iatrogenic. We further propose that the toxicity of these stressors is both cumulative and synergistic.

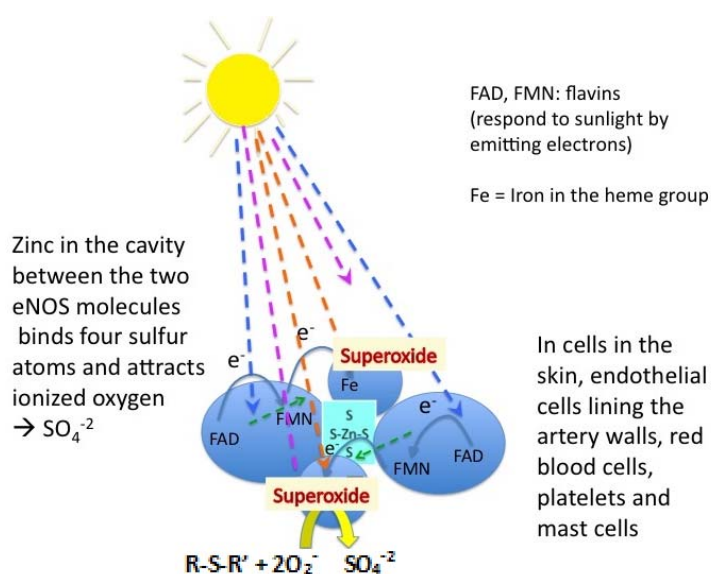
A pioneering study [119] by Gruebele and Havenith in 2008, provided an important new technology, Kinetic Terahertz Absorption (KITA) spectroscopy, which was employed to measure the changing protein-hydration-water dynamics during the fast refolding of ubiquitin. KITA has been shown to be generally applicable to studies of water hydration dynamics and protein folding. These studies [119–125] have revealed that solvent dynamics are coupled to secondary structure formation of the protein. Terahertz (THz) spectroscopy has provided experimental evidence that collective long-range dynamics are a key factor of biomolecular hydration [121]. We suggest that KITA studies of water hydration dynamics may provide additional direct empiric support for our concept of interfacial water stress [IWS]. For example, when a polyanionic osmolyte (sodium citrate) was added to an aqueous solution, long-range collective water dynamics were enhanced [126]. We suggest that the observed long-range collective water dynamics enhancement likely occurred *via concomitant raising of the ZP and lowering of IWS*.

## 2. Results

In this paper, we propose that the biophysical effects of pro-inflammatory cationic surfactants on cell membrane function, mediated by water, provide the provocation that induces SDS. Under our hypothesis, polycationic surfactants are proinflammatory agonists. The downstream anti-inflammatory counter-regulatory effectors, which balance out the hyper-permeable state, are hydrogen sulfide (H<sub>2</sub>S), inorganic sulfate, and the bio-sulfates. The restoration of basal permeability and/or promotion of enhanced barrier integrity are based on adequate sunlight exposure and adequate dietary sulfur, cholesterol, and zinc. Recent studies by Chen and Mehta and Kleinbongard demonstrated that human erythrocytes possess an active and functional eNOS that is located within the plasma membrane [127,128]. It is with these background studies clearly in mind that we are led to introduce here a key

novelty, the “Seneff hypothesis,” the concept that membrane bound endothelial and erythrocytic nitric oxide synthase (eNOS), in the presence of caveolin-1, and sunlight, oxidizes  $H_2S$  to sulfate [114]. See Figure 2. To wit, the zinc-tetrathiolate complex, situated in a cavity formed between the two monomers of the eNOS dimer, is the proposed site of endogenous sulfate biosynthesis, with superoxide being provided for the reaction as a consequence of sunlight exposure to the flavins, FMN and FAD. We propose further that Ch-S, sulfated glycolipids, and sulfated GAGs form as subsequent reaction products.

**Figure 2.** Schematic depiction of membrane bound Nitric Oxide Synthase Producing Sulfate.



We thus propose that eNOS, in addition to its role in producing small amounts of nitric oxide (NO), has a more significant but heretofore overlooked role as a major supplier of sulfate to the extracellular matrix proteins throughout the body. We propose here the novel hypothesis that eNOS is a dual-purpose enzyme, and that, in many cells, its main purpose might be to produce sulfate (an anionic kosmotrope) rather than nitrate (an anionic chaotrope), the ultimate product from nitric oxide. This makes both intuitive and biophysical sense in light of the apparent alignment between cellular Ch-S production and eNOS localization, and the positions of nitrate and sulfate within the Hofmeister series [16]. Under pathological conditions, when excess calcium enters the cell due to stressors, eNOS detaches from the membrane and switches to nitrate synthesis, in order to compensate for the kosmotropic cation (calcium) that is replacing the chaotropic cation (potassium). Aluminum, which is added as an adjuvant to many vaccines, is a much stronger kosmotrope than calcium, and hence has an even more dramatic effect in dislodging eNOS and disabling sulfate synthesis.

Eukaryotic cells have a characteristic negative surface charge established by anionic integral or peripheral plasma membrane components [129]. At physiologic pH in health, both the blood serum ZP and pH are high and the cellular elements of our blood are dispersed and electronegative [130]. The ionic buffering of our blood by inorganic sulfate and the bio-sulfates (sulfatides and sulfamates)—sterol sulfates, sulfated glycolipids, and sulfated GAGs—is essential in maintaining the ZP of our blood [131]. Any event which sufficiently lowers the concentration of sulfate results in colloidal instability of the many macromolecules and cells suspended in our blood.

Below a certain threshold of ZP-lowering, “salting out” of various macromolecules and cells will occur [132]. Such a phase-transition can be fatal. Platelets release thrombin and thromboplastin to restore hemostasis via clot formation. Albumin provides electrostatic stability to our blood and buffers the effect of exogenous cations and polyelectrolytes [133]. With age, our blood albumin levels decline. This decline shifts the balance between blood clotting and blood dispersion towards clotting. Both mercury and aluminum bind strongly to cysteines in serum albumin in the blood stream [134,135]. The absorption of aluminum onto serum albumin has a profound effect on ZP [134], driving it even to positive values at physiologic pH with sufficient concentrations of aluminum hydroxide. It is believed that much of the mercury that is filtered into the proximal tubular lumen in the glomerulus of the kidney is present primarily as a conjugate of albumin, bound to the sulfhydryl group of a cysteine molecule [135]. Thus, positively-charged mercuric  $Hg^{2+}$  salts bound to serum albumin would be expected to cause a similar effect as aluminum on serum ZP.

### *2.1. Stress Induced Breathing Patterns Following Vaccination*

“Stress”, according to Hans Selye, is “the sum of all nonspecific changes caused by function, damage, or the rate of wear and tear in the body. In simple terms: the common results of exposure to anything” [2]. We propose that interfacial water stress [44] triggers the non-specific stress adaptation syndrome, resulting in the stereotyped, biophysically-determined phenomena, e.g., THP-G, and SSP-G, so well-described by Selye [3] and others, which are ultimately responsible for the “pluricausal diseases”. All stressors have the potential to produce the characteristic manifestations of an “alarm reaction”. Alarm reactions are not due to distinctive actions but to the stressor property that they share—the ability to induce interfacial water stress [44].

Stress-induced respiratory pattern changes have been reported in asthma [136], pulmonary microembolism [137], pulmonary inflammation [137], septicemia [138,139], myocardial infarction [140], brainstem infarction [141], preeclampsia [142,143], eclampsia [135], and anaphylactic shock [144]. Emotions and stress are known to change the respiratory pattern [136,145,146]. The breathing control centre of the brain is in the respiratory centre located in the lower part of the brain stem called the medulla oblongata.

According to Dr Viera Scheibner, SIDS researchers refer to all the events where a child is breathing very shallowly, but not dying, as “false alarms” with regard to SIDS. Instead of deeming such events as insignificant, Dr Scheibner used a computerized breathing monitor to study them, recording the babies’ breathing longitudinally over weeks on end. She maintains that overnight six to eight hour studies, often used in SIDS research, are very misleading [11–15]. Through non-stop hour by hour recording of babies’ breathing for up to 5 1/2 months, both apneas (pauses in breathing) and hypopneas (a stress-induced shallow, low volume breathing pattern) can be demonstrated, all of which showed increased stress patterns after vaccinations. The time frame for these stress patterns has been described by Dr Scheibner as the “critical days” [12]. According to Dr Scheibner, the pattern of breathing of babies after vaccinations shows an alarm reaction within one to two days, which may be biphasic, followed by the stage of resistance around day 5 to 7, and finally the stage of exhaustion around day 16 [15,147].

## 2.2. Hofmeister Effect

Hofmeister [16,24,148] showed that neutral salts varied in their effect on the solubility of proteins. One group of salts could be ranked according to their efficiency at *precipitating* proteins, while a second group could be ranked according to their efficiency at *solubilizing* proteins. The Hofmeister ionic sequence has been thought of as ranging from stabilizing “kosmotropes” to disruptive “chaotropes.” The structure-making (kosmotrope) and structure-breaking (chaotrope) influence of ions on the hydration water has been basically understood as arising from a balance between the water-water and ion-water interactions, which vary considerably with the charge density on the solute surface. Different salts have different efficiencies in salting-out proteins, while some salts have no effect. Most importantly, the effectiveness of the anions and cations seems to assume a particular specific order. The Hofmeister series has been speculated to reflect different ordering powers of ions on the surrounding water molecules. There is ample evidence supporting the importance of hydration effects beyond the first hydration shell [40,43,149–157]. The structure and dynamics of interfacial water molecules are different from those in the bulk and exhibit specific ion effects [40,43,158–163].

## 2.3. Serum Albumin and Zeta Potential

One of the main functions of serum albumin is to control colloidal stability in the blood [133]. The hypoalbuminemia of aging and the hypoalbuminemia of end stage renal disease potentiate coagulation by cationic electrolytes and/or polyelectrolytes. Cells and complex molecules suspended in the blood avoid agglomeration through a negative charge field maintained in the immediate surrounding space. The rate at which a charged particle suspended in a medium will travel in an applied electric field is an important measure of colloidal stability in the medium, and is associated in physics with Zeta Potential (ZP) [130]. A high negative value for ZP is essential for maintaining blood as a colloidal suspension [164]. In 2010, Tigrek and Barnes (p. 35) defined ZP more specifically as “the electrical potential drop from the particle surface across the bound fluid, to the interface where the liquid begins to flow under the shear stress. Stated another way, the ‘zeta potential’ is the potential at the surface boundary between the stationary fluid and the liquid that is moving with the particle” [165].

## 2.4. Origin of the Surface Charge

Most particles in an aqueous colloidal suspension carry an electric charge. There are many origins of this surface charge depending upon the nature of the particle and its surrounding medium. Some of the more important mechanisms include ionization of surface groups, differential loss of ions, and adsorption of charged species. Surfactant ions may be specifically adsorbed onto the surface of a particle. Anionic surfactants would lead to a negatively charged surface, whereas cationic surfactants would lead to a positively charged surface. Most cells of eukaryotic origin have a net negative surface charge from anionic plasma membrane components [129,130]. This charge distribution is thought to be important in the movement of various macromolecules across cell membranes.

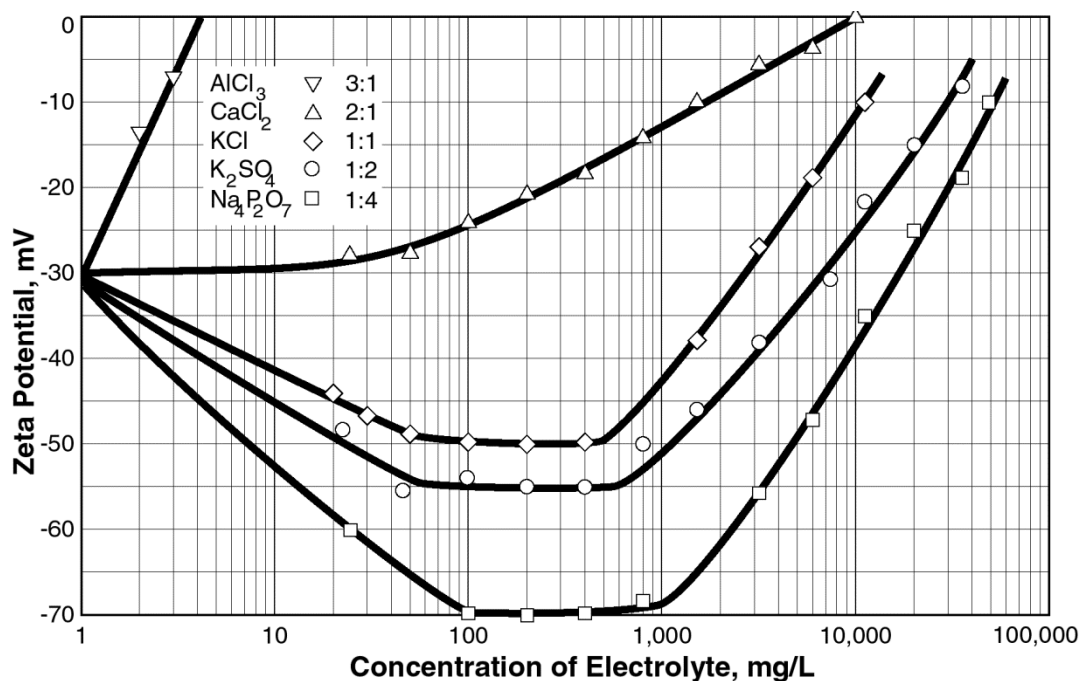
### 2.5. Surfactant-Induced Interfacial Water Stress

Riddick found a minimum in the ZP enhancement at low concentrations, e.g., 100 parts per million, of potassium sulfate, in an anionic colloidal suspension of Minusil [132]. See Figure 3. Jones and Ray observed a minimum in the surface tension of electrolyte solutions at around 1mM concentrations [166] using the capillary rise method. See Figure 4. At that time, the ‘Jones-Ray Effect’ was essentially dismissed as an artifact of the indirect experimental method used. However, in 2004, Petersen *et al.* [167,168] presented direct experimental confirmation of the enhanced anion concentration around 1 mM. See Figure 4. Interestingly, the human arterial plasma concentration of inorganic sulfate is 0.5 mM [169]. *We do not believe that this concentration is accidental.* This sulfate concentration is found at the minima for both ZP enhancement and surface tension enhancement. Our blood is a predominantly-anionic colloidal suspension. Sulfate is a kosmotropic dianion at physiologic pH. We propose that interfacial inorganic sulfate and the bio-sulfates, at comparable conditions (similar pH, time, temperature, and electrolyte concentrations), lower both the serum and the plasma dynamic surface tension of human blood, *in vivo*. The net effect is to stabilize colloidal suspensions, membrane function, protein function, and cellular function. We surmise that elevated plasma bio-sulfate concentrations in X-linked ichthyosis and liver cirrhosis represent lowered bioavailability, probably related to concentrations of bio-sulfates which exceed the low millimolar concentrations at which the Jones-Ray surface enhancement and Riddick ZP enhancement are likely to occur [76,170]. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity and sterol synthesis by Ch-S has been shown in cultured fibroblasts [171]. We suggest that this observation represents a non-specific surfactant effect of the sterol sulfate mediated by interfacial water stress found on the “upslope” of the Jones-Ray and Riddick curves [132,166,172,173].

According to Collins [40,43,152], Von Hippel *et al.* [174] and Dos Santos *et al.* [175,176] proteins are stabilized by high concentrations of strongly hydrated anions and destabilized by high concentrations of weakly hydrated anions or strongly hydrated cations. Stabilization and, in the extreme case, crystallization, are associated with a decrease in the solvent accessible surface of a protein, induced by kosmotropes, whereas destabilization, and, in the extreme case, solubilization, are associated with an increase in the solvent accessible surface. Protein structure is destabilized and function is impaired by cationic electrolyte and polyelectrolyte surfactants, mediated by interfacial water stress [20,21,29,40–44,85,148–158,174–184]. Solutes have effects upon the structure of water which extend far beyond the first two hydration shells [149–157,185–187].

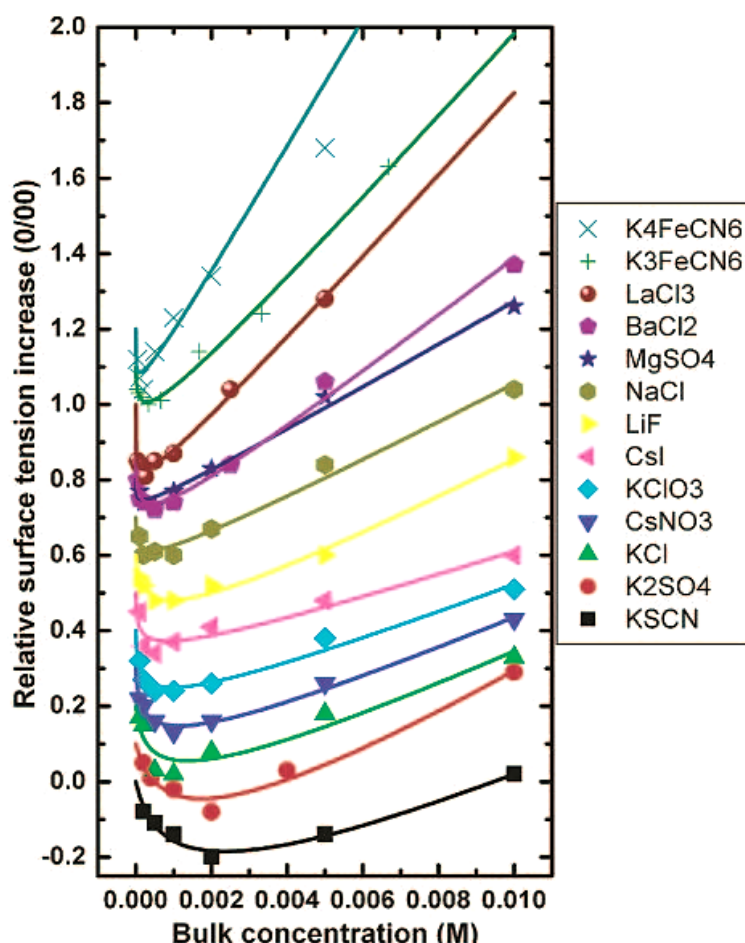
Kosmotropic cations and chaotropic anions increase the viscosity [152] and surface tension [148,175–177,189–191] of water, as well as lowering the ZP and the pH, and increasing aggregation and cell-cell adhesion, properties that could lead to catastrophic changes in blood serum if left unchecked. For example, there is evidence that the blood surface tension shows higher values for patients with acute myocardial infarction compared to the control group [54]. The surface tension of erythrocytes obtained from untreated cardiac arrhythmia patients also tends to be higher than that of treated patients [45].

**Figure 3.** Zeta potential data for various electrolytes in an anionic colloidal suspension of 100 ppm Minusil [132]. Data were originally published per Thomas M. Riddick (1968) in [132] and are reproduced here with permission of Zeta-Meter, Inc. (Staunton, VA, USA).



Wu *et al.* reported linkage between ZP and electron donicity of charged polar surfaces [192]. Plurivalent counterions are well-known flocculents, making the polar surfaces more hydrophobic. Yoshisuke [71], and others [97,98,193], have shown that the Shwartzman reaction induces thrombus formation and hemorrhagic necrosis [71]. How the molecular and humoral immune responses are converted into mechanical and physical phenomena in the circulation remains unclear. It is the authors' opinion, that neither humoral nor cellular immune responses are fast enough to explain the rapidity in which SDS has been reported to occur, unless there has been previous sensitization. Even the substantial mobility of Ch-S, attributable to its amphiphilic character, is not likely sufficient to completely explain the connectedness and rapidity of the reaction in SDS. Rather, we believe that the branching (avalanche-like) chain of reactions leading to SDS can only be explained by invoking the direct involvement and intermediacy of interfacial water. The provocation in SDS is the inducement of interfacial water stress by exogenous environmental "stressors". Sometimes the exogenous interfacial water stress (EIWS) is of sufficiently great degree that prior sensitization is not a necessary prerequisite to SDS. Serum surface tension is transiently elevated after provocation injection for the Shwartzman reaction, and the coefficient of foaming is simultaneously reduced at the site of the hemorrhage caused by the sensitization injection [71]. In addition, it was found that the interface viscosity of serum and vascular endothelium is greater when interfaced with sensitized endothelium than with normal endothelium. We hypothesize that these vascular changes may be due to a breakdown of the sulfated glycocalyx following the sensitizing event.

**Figure 4.** Surface tension data for all 13 Jones-Ray electrolyte solutions. The points are the original data from 1937 by Jones and Ray [166]. The change in the surface tension of all 13 Jones-Ray salts were fitted to a simple model by Petersen and Saykally [167,168,188]. Good agreement was found with even larger surface adsorption energies as determined in second harmonic generation (SHG) experiments in the ultraviolet range. Reproduced here with permission from *Journal of the American Chemical Society* [188]. Copyright 2005 American Chemical Society.



Interfacial water accounts for some 70 percent by weight of most organisms, including human beings, making organisms effectively liquid crystalline [185,194]. Most if not all water in living organisms is interfacial water, as it is almost never further away from surfaces such as membranes or macromolecules than a fraction of a micron. Intracellular water is interfacial water [194–196]. Extracellular and interstitial water are substantially interfacial water as well. The vascular system acts as though it were a single organ [1]. Parenteral administration of certain polycationic ions with high charge densities, described as strong kosmotropic cations, affects the entire vascular system. This effect is mediated by interfacial water.

The rate of surface tension lowering of anionic surface-active agents by electrolytes is largely determined by the charge of the added positive ion [197]. When an ionic surfactant is used to produce bubbles [198], the sign of microbubble charge is determined by the polar head of the surfactant. The charge of bubbles exhibits “*unusual positive surface charge characteristics*” in solutions of trivalent aluminum cations [199]. Analysis of their results indicated that the reversal of bubble charge can be

attributed to specific adsorption of  $Al^{3+}$  and its hydroxo complexes at the gas-liquid interface in the low pH range and to precipitation of aluminum hydroxide in the intermediate pH range. In the presence of nonionic surfactants, bubbles can be charged either positively or negatively depending on the pH, and the isoelectric points appear to be related to the oxygen-to-carbon ratio of the surfactant molecule [198].

In 1996, Weissenborn studied the surface tension of aqueous solutions of simple inorganic electrolytes [189]. Results were analyzed in terms of surface tension/electrolyte concentration gradients and this parameter was found to correlate with the entropies of ion hydration, Jones-Dole viscosity coefficients and dissolved oxygen gradients. The concentration of salt in our bodies corresponds to the minimum required for optimal prevention of bubble coalescence [200–202]. As small bubbles are much less harmful than large bubbles, this fact is crucial [203–205]. pH sensitive phase transitions have been suggested as mechanisms for cellular action [159]. The “autothixotropy” of water is thought to possibly play an important role in proton transfer in living beings [206]. Solute-free “exclusion zones,” a general feature of water adjacent to hydrophilic surfaces, were first reported four decades ago [207] by Green *et al.* pH measurements show an extreme drop of pH immediately beyond the exclusion zone, often to less than pH 3 [154–161]. Variation in the size of the exclusion zone with charge, pH, and solutes, reported by Zheng and Pollack in 2003, is consistent with a water-structuring hypothesis [208] which may involve as many as  $10^6$  solvent layers. We suggest that KITA studies may enable further experimental validation of the formation of such massive Exclusion Zones [154].

## 2.6. Zeta Potential and Cardiovascular Disease

There is a close relationship between inflammation, intravascular coagulation, and cardiovascular disease. We propose that the underlying reason is that all three processes are driven by the colloidal instability of the blood associated with abnormally low ZP. We propose that the earliest events in the inflammatory process are characterized by ZP lowering, increased water stress, cell membrane dysfunction [29,156,157], and hemostatic [3] and immune derangement [3,209–214]. Inflammation and serum sickness can be thought of as an unstable dispersion state of our blood, which has an increased tendency to aggregate, flocculate, gelate, hemorrhage, and coagulate [3,209–214]. This unstable state is manifest clinically as acute coronary syndromes, transient cerebral ischemic events, myocardial infarctions [211,212] and cerebrovascular accidents [211,215]. It is known that static surface tension of blood (49–50 Din/cm<sup>2</sup>) is normally lower than the surface tension of water or normal saline solution (approx. 72 Din/cm<sup>2</sup>). An increase in blood surface tension during acute myocardial infarction has been observed in humans [54], a difference that was significant ( $p < 0.05$ ). It was suggested that the increasing surface tension of blood results in rheological disturbances leading to heart failure during acute myocardial infarction.

Sherman (1981) has argued through simple physical considerations based on Laplace’s equation of capillarity, that blood will flow out of capillaries into both the arteries and the veins when the surface tension is too high in the capillary, due to the inverse relationship between the size of the vessel and the pressure [216]. “Critical closure” is a term which describes the phenomenon of flow cessation in the presence of a positive perfusion pressure gradient. Sherman’s use of the term “critical closure”, may be slightly misleading because “closure” seems to imply a “collapse” of capillary lumen. It might be more



accurate to say irreversible “critically-arrested capillary flow”, especially if RBCs, proteins, and bodily humors become “trapped” within the capillary lumen, as is likely to occur, for example, in the “no reflow” phenomenon. Perfusion is strongly dependent on interfacial tension at the microvascular level because capillary interfacial tension, if high enough, can not only reduce capillary flow, but also lead to flow reversal, and eventually to emptying of the capillary and collapse or arresting of flow. The suggestion was made that factors affecting the surface tension of blood to decrease the interfacial tension between blood and endothelium may be clinically beneficial [216].

The term microvascular disease refers to the damage that occurs to the smallest blood vessels throughout the body, including the vital organs (e.g., heart, brain, kidneys, liver). It usually affects the whole body to some degree. The small blood vessels of the eye, the kidney and of the sheaths around the nerves, are often at great risk in diabetes, *i.e.*, risk for the development of diabetic retinopathy, nephropathy, neuropathy. Interestingly, cardiac syndrome X, sometimes referred to as microvascular angina, often has associated findings of *systemic* microvascular dysfunction [217] to strongly suggest that microvascular dysfunction is a systemic malady. While vascular complications of diabetes are often attributed to loss of nitric-oxide-mediated vasodilation, we suggest an alternative pathophysiology: impaired microvascular perfusion due to (a) decreased fluidity and deformability of the RBC membrane related to bio-sulfate deficiency in the endothelial glycocalyx layer (EGL); and (b) increased capillary endothelial interfacial tension. That is, we suggest that the vascular defect in diabetes is more a problem with elevated capillary endothelial interfacial tension [216] and poorly deformable RBCs, than it is a problem with loss of nitric-oxide mediated vasodilation.

The respiratory and auditory centers [218,219] in the brainstem are vulnerable to microvascular ischemic stress. So too is the pancreas [220–225]. Watershed and terminal vascular distributions are particularly susceptible to microvascular ischemic stress [223–225]. These vascular distributions would be predicted to be highly susceptible to pathologic inflammatory stimulation and thrombohemorrhagic phenomena [3] induced by zeta potential-lowering and interfacial water stress-inducing properties of cationic kosmotropic electrolytes and polyelectrolyte surfactants. Dr Mohammed Al-Bayati’s histopathologic analyses of SIDS [220–222] and so-called Shaken Baby Syndrome (SBS) victims [226] are most informative. Al-Bayati’s work provides strong support for the view that microvascular ischemia plays a central role in the pathophysiology of SIDS and, by inference, all SDS events [220–222]. Surfactant-induced water stress [29,40,43,45,54,174,178,211,212], especially that associated with polycationic surfactants, is an important determinant of risk. Any exogenous food, chemical, or biological exposure which lowers blood pH and ZP is also a risk factor. Risk factors for SDS are synergistic and cumulative. Expressed most simply, anything that perturbs the ZP toward less negative values and/or induces cationic kosmotropic or anionic chaotropic water stress represents a step in the direction of enzyme inhibition, protein dysfunction, cellular dysfunction, flocculation, gelation, coagulation, microvascular ischemia, cellular anoxia, infarction, and death. Transcytosis, both endocytosis and exocytosis, membrane potentials [219,227], and ion channels are all profoundly disrupted by polycationic surfactants [31,89,228–231]. A very relevant example is aluminum ( $\text{Al}^{3+}$ ), a kosmotropic trivalent cation, which is a potent and irreversible blocker of voltage activated calcium channels in mammalian neurons [31,228]. Ca-ATPase, protein kinase C and calmodulin (CaM) are biological systems known to be disrupted by aluminum [37,87,178,232]. Another very relevant example is mercury ( $\text{Hg}^{2+}$ ), a kosmotropic divalent cation. It has been shown in infant monkeys that the

ethylmercury in thimerosal is more readily stored as inorganic mercury ( $\text{Hg}^{2+}$ ) in the brain than is orally-delivered ethylmercury and that inorganic mercury tends to linger longer in the tissues [231].

Thus, the sudden death syndrome can now be defined as an acute disruption of the colloidal stability of the vascular system, which triggers a cascade of events [97–100,229,230] leading to death, whenever compensatory mechanisms to maintain colloidal stability of the blood are insufficient. If compensatory mechanisms are sufficient, the cascade can instead lead to a new equilibrium. Mucopolysaccharides, also known as glycosaminoglycans (GAGs), contribute to the inflammatory state of the Shwartzman phenomenon [233–236]. Upon exposure to systemic stress, increases in sulfomucopolysaccharide incorporation occur throughout the body, and this is designated as the “universal nonspecific mesenchymal reaction” [3].

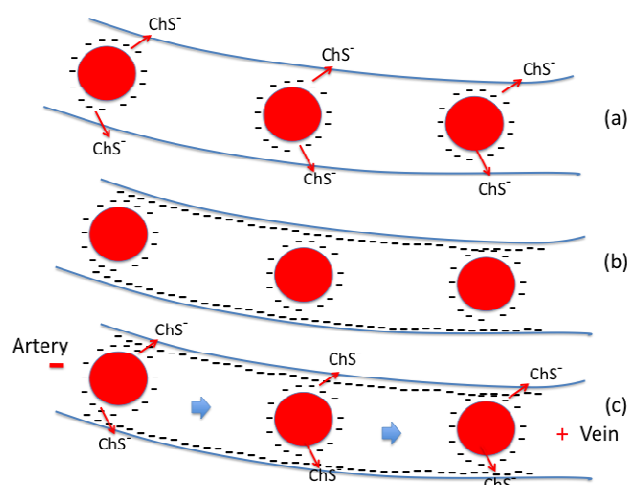
Examples of sudden death syndrome from the medical literature support our hypothesis, including thrombohemorrhagic phenomena (THP), such as anaphylaxis [229,230,237–239], disseminated intravascular coagulation (DIC) [240,241], HELLP syndrome [242], acute liver necrosis [243], Waterhouse–Friderichsen’s syndrome, hemolytic uremic anemia, idiopathic pulmonary hemorrhage [244], acute pancreatitis [245], acute pituitary necrosis [246], pseudomembranous colitis, thrombotic thrombocytopenic purpura (TTP), Sanarelli-Shwartzman phenomenon (SSP), Henoch-Schonlein purpura (HSP), eclampsia [238], serum sickness, hemolytic anemia, preeclampsia, and stillbirths [247].

### *2.7. The Role of Bio-sulfates in Maintaining Cell Membrane Function*

Adequate endogenous and dietary cholesterol is essential in maintaining proper cell membrane function [114–117], as is adequate endogenous and dietary sulfur [114,118]. The surface charge of RBCs plays a significant role in cell-to-cell interactions [248]. We propose that it is primarily the negatively-charged sulfate head-groups imparted to RBC and endothelial cell membranes that are responsible for both their net and specific surface charge [130]. We propose that this is one of the mechanisms by which cell membranes are able to store energy [249–252]. The amphiphilic property of Ch-S endows it with extremely facile, dynamic intercellular and intracellular mobility. We further suggest the novel concept that RBCs may actually discharge negative charge by unloading sulfate onto the endothelial wall, as illustrated in Figure 5. In part due to their higher concentration of  $\text{CO}_2$ , veins are more acidic than arteries, which suggests that there is an electric field that would propel negatively charged particles in the capillaries towards the veins. This process would be renewable as the RBCs travel through superficial veins, regenerating their supply of Ch-S through a process catalyzed by sunlight exposure [114,116,253].

The electrostatic charge-charge repulsion of the negatively-charged Ch-S and GAG head-groups in the outer membrane are the primary determinants of viscosity of membrane lipids in both eukaryotes and prokaryotes. The ZP is of critical importance to maintenance of membrane viscosity in all cells.

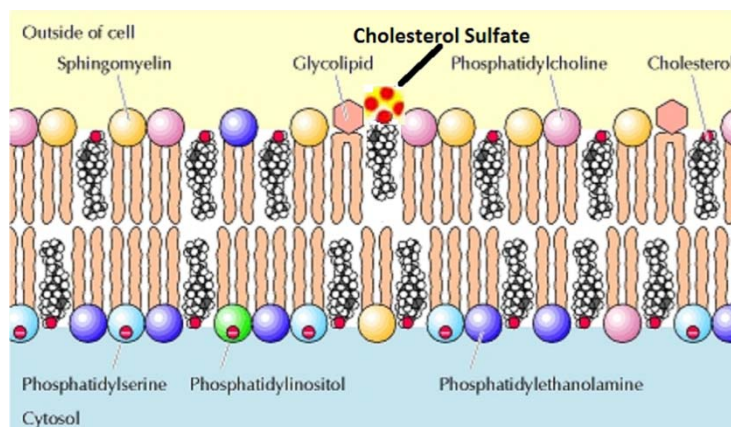
**Figure 5.** A proposal: (a) RBC loses charge through capillary, (b) Negative charge builds on artery wall, (c) Battery poles are thus maintained between artery and vein.



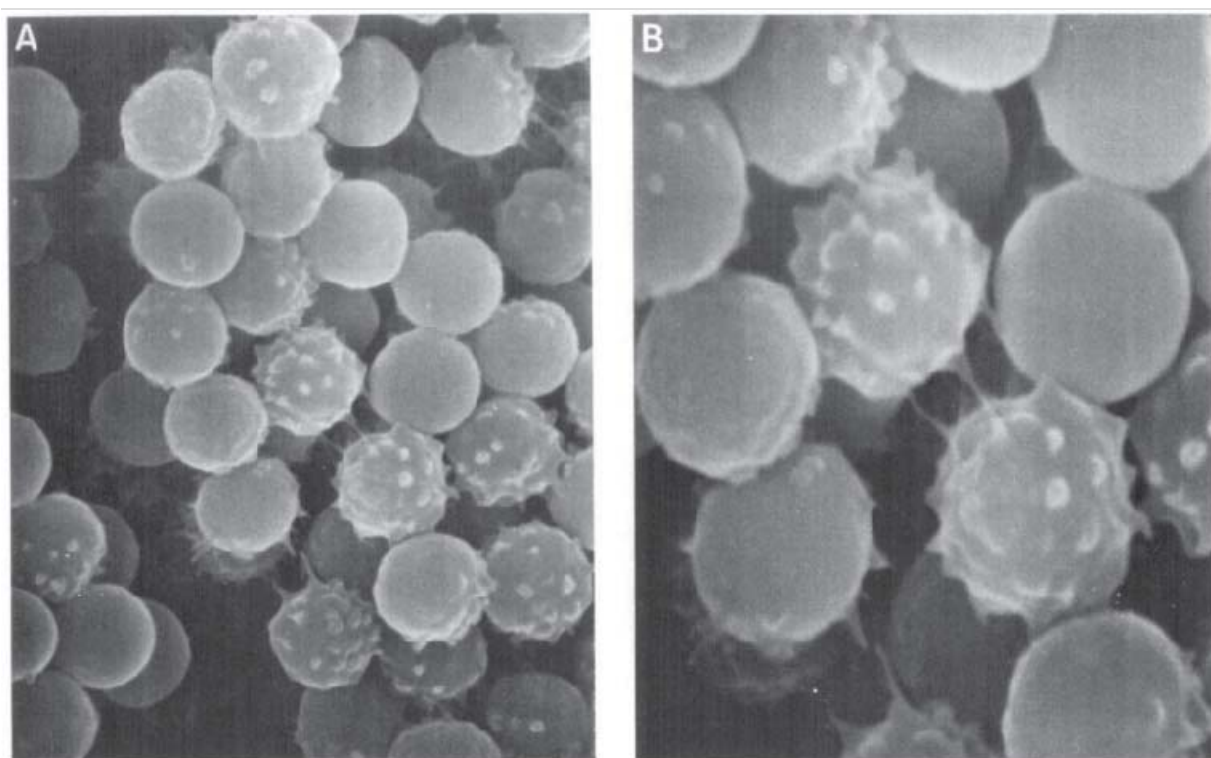
We hypothesize that the cumulative ZP-lowering effect of serial vaccination with polycationic surfactants lessens microvascular perfusion throughout the entire body, especially in the terminal watershed vascular distributions. Sulfated glycolipids and sulfated GAGs are ubiquitous and undoubtedly play very important roles in life [254–257], along with the sterol sulfates. These bio-sulfates generate the net surface charge density, as well as the specific surface charge density, and are determinants of bio-membrane viscosity and permeability. For instance, histochemical, autoradiographic, and histologic studies by Horn *et al.* suggest that a sulfated mucopolysaccharide, possibly of leukocytic origin, is a component of the fibrinoid thrombi of the generalized Shwartzman reaction [233–236].

Due to its ionic charge and amphiphilic property, Ch-S is far more agile than cholesterol in entering plasma membranes. Its rate of inter-membrane exchange is approximately ten times faster than that for cholesterol [258,259]. The biosynthesis, properties, and function of Ch-S are not yet fully described. Ch-S has been hypothesized to play an important role in capacitation of human spermatozoa [260–264]. More recently, sterol sulfates have been shown to play a role in synaptic function [264–266]. Sulfated neurosteroids have been shown to be potent non-competitive antagonists of GABA<sub>A</sub> receptors without a clear structure-activity relationship [266]. Ch-S is found in relatively large amounts in RBC's where it is known to play a role in osmosis. Its presence induces a change in shape from discoid to echinocytic, caused by the tendency of Ch-S to migrate to the outer membrane layer [267]. An impairment in such deformability due to glycated hemoglobin is associated with diabetes [268]. In canine blood, Ch-S has been shown to lessen hemolysis and stabilize RBCs [269]. Scanning electron microscopy has demonstrated stabilization by Ch-S of the normal biconcave shape of the human RBC [270]. Ch-S was shown to protect the human RBC against hypotonic hemolysis. At physiological concentrations of Ch-S, the sulfate moiety, as well as the side chain of Ch-S, were both shown to be necessary to biological activity *in vitro* [271]. Figure 6 shows a graphical depiction of cholesterol sulfate in the red blood cell membrane, and Figures 7 and 8 show how the shapes of red blood cells change under the influence of Ch-S.

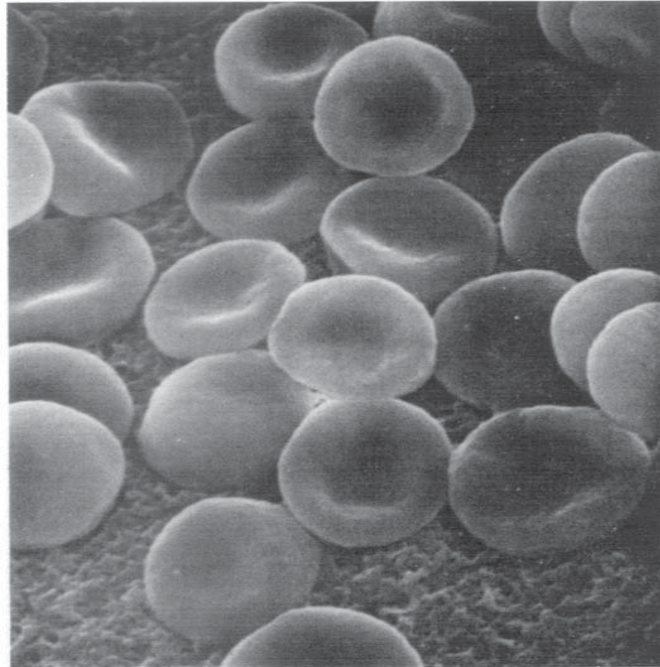
**Figure 6.** Graphical depiction of cholesterol sulfate in the red blood cell membrane. Adapted from Cooper and Hausman: *The Cell: A Molecular Approach, Fifth Edition*, [272] by permission of the publisher.



**Figure 7.** (a) Scanning electron micrograph of human erythrocytes in hypotonic saline solution.  $\times 10,000$ ; (b) Scanning electron micrograph of human erythrocytes in hypotonic saline solution.  $\times 20,000$ . Scans were originally published by Bleau *et al.* [271] and are republished here with permission of the publisher.



**Figure 8.** Scanning electron micrograph of human erythrocytes in hypotonic saline solution in presence of  $10^{-5}$  M cholesterol sulfate.  $\times 10,000$ . From Bleau *et al.* (1975) [271] with permission of publisher.



### 2.8. The Major Determinants of RBC Deformability

The major determinants of RBC deformability include cell geometry, cell shape and internal viscosity (*i.e.*, mean cell hemoglobin concentration and components of the erythrocyte membrane) [273]. Blood flow in the microvasculature and the large arteries depends on erythrocyte deformability. Fluidity of the RBC membrane and RBC deformability is decreased in patients with diabetes mellitus. Dondorp *et al.* showed that RBC deformability is a predictor of anemia in severe falciparum malaria. RBCs with reduced deformability are more likely to be cleared from the circulation by the spleen, a process that is augmented in acute malaria. Since the majority of RBCs even in severe malaria are uninfected, the reduction in RBC deformability in the patients resulted mainly from changes in the unparasitized erythrocytes, *i.e.*, due to a systemic response. Impairment of microcirculatory flow by rigid red blood cells is suggested by the strong correlation of mortality with RBC deformability at a lower shear stress corresponding to that encountered in the capillaries [274].

Babu demonstrated a significant decrease in RBC deformability and increase in shape parameters in diabetes with hypercholesterolemia [275] which might increase microcirculatory complications compared to diabetes with normal cholesterol. Condon *et al.* demonstrated that intravenously injected mesenteric lymph produced during hemorrhagic shock decreased RBC deformability in the rat [276]. The *in vivo* inhibition of inducible nitric oxide synthase (iNOS) did not prevent lymph-induced RBC injury. These results suggest that this effect is not dependent on activation of the iNOS pathway but seems to require white blood cells (WBCs). Zaets *et al.* showed that interruption of lymph flow from the gut into the bloodstream by lymph duct ligation prevents trauma/hemorrhagic shock-induced RBC damage. Because decreased RBC deformability contributes to impaired perfusion of the microcirculation,

preservation of RBC deformability may decrease the incidence of trauma/hemorrhagic shock-induced organ dysfunction [277].

Important parameters of erythrocyte function and integrity are thought to be negatively affected in Alzheimer's disease (AD) patients. Vascular abnormalities in AD have been implicated by growing evidence. Altered RBC morphology and reduced RBC deformability of RBCs is a highly suspect vascular abnormality in AD [278]. Interestingly, amyloid beta protein ( $A\beta$ ) has been identified in extraneuronal tissue, including RBCs and brain capillaries. Misiti *et al.* very recently demonstrated that  $A\beta$  exposure results in a decrease in the immune staining of erythrocyte eNOS with concomitant alteration in RBC morphology, decreases in nitrite and nitrate levels, and alteration in membrane acetylcholinesterase activity [279]. The alteration in RBC morphology was reported to take place at just 10  $\mu$ M  $A\beta$  concentrations. This observation begs the question as to what effect, if any  $A\beta$  concentrations have on the measured ZP and interfacial tension of the blood of AD patients. That is, do the known neurotoxic effects of  $A\beta$  depend, at least in part, on induction of interfacial water stress? Conceivably, a KITA study of  $A\beta$  in the presence of a suspension of RBCs from control subjects compared to that of AD patients *might* be informative, with respect to the induction of morphologic and functional alterations in the RBCs. Neurologic phenotypes have been associated with RBC acanthocytosis [280]. RBC acanthocytosis, *i.e.*, deformed erythrocytes with spike-like protrusions, coincides with nervous system abnormalities and comprise a heterogeneous group referred to as the neuroacanthocytosis (NA) syndromes [281].

### 2.9. Acute Shock and Role of Endothelial NOS-derived NO in SDS

Anaphylactic shock is a sudden, life-threatening allergic reaction associated with severe hypotension. Platelet-activating factor (PAF) is implicated in the cardiovascular dysfunctions occurring in various shock syndromes, including anaphylaxis. Anaphylactic shock is especially associated with quadrivalent HPV vaccine, which contains aluminum hydroxide. Based on the number of confirmed cases, the estimated rate of anaphylaxis following quadrivalent HPV vaccine was significantly higher than identified in comparable school-based delivery of other vaccines [282].

In this review, we have described several of the adverse biophysical properties associated with cationic surfactants,  $Al^{3+}$  salts, and non-ionic surfactants. The U.S. CDC VAERS database provides considerable evidence of life threatening anaphylactic shock and anaphylactoid events associated with HPV vaccine, as well as with all of the aluminum (3+) containing vaccines, some of which resulted in sudden death. The U.S. CDC Vaccine Excipient & Media Summary states, "Excipients are inactive ingredients of a drug product necessary for production of a finished pharmaceutical formulation." In the February 2012 update, the CDC disclosed that excipients in U.S. HPV vaccine include amorphous aluminum hydroxyphosphate sulfate, polysorbate 80, and sodium borate (from the manufacturer's package insert of March, 2011). The relevance to SDS is apparent from reports of unexplained deaths of some women attributed to HPV vaccines in the CDC VAERS database, some of which were described variably as death during sleep or while bathing. A reasonable question should be raised as to the purported safety and alleged biologic *inactivity* of the ingredients in the HPV vaccine, particularly aluminum, polysorbate 80, and sodium borate. Moreover, a further reasonable question should be

raised as to the purported safety and alleged biologic *inactivity* of all of the aluminum and polysorbate 80 containing vaccines. This question may be further explored by analysis of the CDC VAERS database.

For example, CDC VAERS report ID: 337242 states “my daughter had her 3rd GARDASIL vaccine in Sept. She was a very healthy young lady, she went to take a shower and died. Autopsy report states undermined [*undetermined*] death. There was no sign of trauma to the body to indicate a fall. She had pointed the shower head away from her and she got down on her knees and put her head on the edge of the tub and passed away.”

Excessive production of the vasodilator NO causes inflammatory hypotension and shock. It had been generally accepted that transcriptionally regulated NOS (iNOS) was responsible for the NO synthesis. However, Cauwels *et al.* found that anaphylactic shock depends on PI3K (phosphatidylinositol 3 kinase) and *eNOS*-derived NO. In two different models of active systemic anaphylaxis, either *eNOS* deficiency or inhibition of *eNOS*, PI3K, or Akt provided complete protection. Thus, in contrast to the unsubstantiated paradigm that only excessive *iNOS*-derived NO underlies cardiovascular collapse in shock, their data strongly supported the unexpected concept that *eNOS*-derived NO is the principal vasodilator in anaphylactic shock [229]. Duran *et al.* have proposed a putative mechanism by which *eNOS*-derived NO stimulates increased microvascular permeability [230].

In the experiment which demonstrated that *eNOS* was responsible for NO production [225], the conditions inducing anaphylactic shock in mice included aluminum hydroxide adjuvant, as does HPV vaccine. We propose that *eNOS* switches from sulfate to nitrate production under such conditions, after detaching from the membrane at the caveolae. The surfactant aluminium, a highly kosmotropic cation, binds CaM with a much greater affinity than does calcium. Calcium, upon binding to CaM, causes *eNOS* to detach from the membrane, and, following phosphorylation, to produce nitric oxide. We hypothesize that *eNOS* produces sulfate only when it is attached to the membrane, so that, in this way, aluminum interferes with *eNOS*' ability to produce sulfate. Through subsequent systemic depletion of sulfate, this leads inexorably to SDS.

Dianionic inorganic  $\text{SO}_4^{2-}$  raises the ZP and provides the putative obligatory precursor (sulfate) for the bio-sulfates (sulfamates and sulfatides)—sterol sulfates, sulfated glycolipids, and sulfated GAGs—monoanionic (1-) at physiologic pH—which also raise the ZP. The bio-sulfates (sulfatides and sulfamates) are essential in maintaining the ZP, viscosity, permeability barriers of the vascular system, ion channel function, and transcytosis of nutrients and metabolites of our cells. Sulfate is also responsible for binding to cationic toxins like mercury [98] and aluminum and expelling them through the kidneys. Such action would however also lead to a further reduction in the *bioavailability* of sulfate. X-linked ichthyosis and liver cirrhosis are examples of two clinical conditions in which plasma bio-sulfate levels are elevated, but unavailable, biologically [76,170].

The formation of sulfate by *eNOS* results in an immediate increase (to more negative values) in the ZP [132], and thus the disruption of this process would lead to further induction of water stress. Within the sheltered environment of the caveolae, within lipid rafts of endothelial, erythrocytic, and neuronal cell membranes, sulfotransferases (SULTs) synthesize Ch-S and sulfated sphingolipids. Any dietary, environmental, or iatrogenic (e.g., parenteral) event that impairs sulfate synthesis by endothelial NOS (*eNOS*) or neuronal NOS (*nNOS*), also impairs bio-sulfate synthesis, thereby immediately altering the junctional proteins between endothelial cells and increasing microvascular permeability. The clinical signs and symptoms of the metabolic syndrome, microvascular ischemia, and endothelial dysfunction

are often seen together in diabetic patients [283], who are highly-prone to multisystemic, end-organ damage involving the retina, kidneys, nervous system, and vascular system. Shedding of the EGL during acute hyperglycemia has been shown to coincide with endothelial dysfunction, including increased permeability of the endothelium, increased reactive oxygen species (ROS), reduced nitric oxide (NO) synthesis, and coagulation activation *in vivo* [272]. It is entirely possible that the underlying, shared, pathophysiology is elevated microvascular interfacial tension [216,284–287], as has been discussed previously. We surmise that an EGL which is depleted in sulfate content has elevated microvascular interfacial tension, a key risk factor for insulin resistance [283,285]. Cationic surfactants generally associate with GAGs, e.g., the EGL of the vascular system [249,250,284–288], disabling their protection against water stress. The process of expelling cationic surfactants via the kidney necessarily further depletes the sulfate supply. The deficit in intramembrane sterol sulfate and sulfated GAGs results in decreased intramembrane viscosity, decreased intramembrane deformability, and increased intramembrane permeability, all of which compromise the stability of the blood colloidal system.

### 3. Discussion

The terms “anaphylaxis” and “allergy” were created by Charles Richet in 1901 and Clemens von Pirquet in 1906, respectively. When Charles Richet attempted to vaccinate dogs to jellyfish (*Physalia*) poison, he provoked a violent reaction that quickly killed the dogs following a second injection. These results were subsequently replicated with the tentacles of sea anemone (*Actinia eqnina*). Remarkably, certain of the dogs experienced no apparent ill effects and survived when they received only a single injection. However, when a repeat injection was given three to four weeks after the first sensitizing (or preparatory) dose, the animals immediately showed serious symptoms of shock: vomiting, bloody diarrhea, dyspnea, incontinence, hypotension, syncope, unconsciousness, asphyxia and death, within 15 to 30 minutes. For this reaction, Richet used a Latin term ana-phylaxis or anti-protection, because the outcome was the opposite from the protection that the vaccine was supposed to provide. In further experiments with numerous other species, including cats, rabbits and horses, Richet showed that anaphylaxis is a universal immune system response [237–239,289]. In 1907, Richet demonstrated what is known as *passive anaphylaxis*. He also established a relationship between leukocytosis and anaphylaxis. He concluded his Nobel Prize lecture in 1913, stating that “anaphylaxis is an universal defence [*sic*] mechanism against the penetration of heterogenous substances in the blood, whence they can not be eliminated.”

At the close of the 1800s, a similar anaphylactic phenomenon, serum sickness (“Serum-Krankheit”), was a common outcome in children subjected to injections of the first mass preserved, hypodermically delivered injections of sera for scarlet fever, tetanus and diphtheria. The symptoms observed included urticaria, erythema, pangs of pain, itching, and in the worst cases near-syncope, with nausea, vomiting, hyperthermia, edema over the whole skin area and general urticaria. Viennese pediatrician Clemens von Pirquet introduced the Latin derived term “allergy” in 1906, to better describe this “altered reactivity” to the sera [290]. With it he wanted to describe in general a change in reactivity of the organism, namely in time, quality and quantity. Prior to advent of vaccination, mass allergy such as serum sickness was unknown. According to allergist Warren Vaughan, “serum disease,



as this is called, is a man-made malady. If we had no curative serums and if there were no such thing as a hypodermic syringe with which to introduce the material under the skin, there would be no serum disease.” Hence, serum sickness is iatrogenic disease [290,291].

Based on extensive review of the scientific literature, we propose in this paper that any exogenous substance that lowers the ZP, and/or introduces polycationic kosmotropic interfacial water stress, and/or lowers the bio-sulfate level, increases the likelihood of sudden death, by triggering a cascade of events in the pathogenesis of inflammation, allergy, infection, thrombosis, hemorrhage, ischemia, infarction, anaphylaxis, disease, and death. Inflammation, allergy, anaphylaxis, and serum sickness should be redefined to reflect this reality. A novel hypothesis as to the etiology of sudden death syndrome is presented which looks specifically at the very earliest events in the pathophysiology of SDS. In most instances, introduction of polycationic surfactants into our bloodstream causes acute interfacial water stress, lowering of ZP, lowering of pH, elevation of viscosity, and electrohemorheologic—hemodynamic derangement. This triggers a cascade of immunologic and hemostatic events, leading inexorably to tissue hypoperfusion, cellular anoxia, seizures, arrhythmias, infarctions, cardiovascular collapse, and death [97–100,209,229,230,237–239].

A biophysically-based disruption of blood flow seems likely to be involved in SDS. Seizure activity or cardiac arrhythmias, sometimes both, often accompanies SDS. Shock, either cardiogenic or anaphylactic, followed rapidly by cardiovascular collapse, e.g., with froth at mouth, is often the initial manifestation of SDS. Rudolph Virchow originally proposed, in 1856, that vascular events are a common pathophysiology for deaths and disease [292]. More recently, postmortem studies [220–222] of SIDS victims commonly use the word “ischemic,” as in “ischemic changes,” on histopathology analysis. Thrombohemorrhagic phenomena, e.g., disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic, inflammatory, and anaphylactic events, have all been associated with SDS. Thus, in the authors’ opinion, an acute vascular ischemic etiology is strongly favored as the central common pathophysiology of SDS. We propose that the initial events in SDS are universally vascular events. These hemorheologic events trigger a cascade of immunologic and hemostatic consequences, leading rapidly to death. They are “sparked” by exogenous polycationic surfactant-induced water stress. They are biophysical in origin and have profound hemodynamic consequences.

We hypothesize that acute lowering of the ZP can result in an acute increase in endothelial cell permeability and acute alteration in RBC morphology from dispersed biconcave discs to adherent rouleau formations [248], echinocyte, stomatocyte, acanthocyte, and spherocyte transformations [113,293–306], with consequent elevation in blood viscosity, elevated resistance to microvascular blood flow, diminished oxygen transport, and diminished oxygen delivery. CO<sub>2</sub> overload is a secondary inevitable consequence of the acute colloidal instability of our blood induced by the ZP-lowering, polycationic surfactant stress. Acute colloidal instability of flowing blood impairs perfusion to the brainstem respiratory and auditory centers. Flowing blood has electrokinetic, hemodynamic, and hemorheologic properties which are substantially affected by polycationic surfactant water stress. Our entire vascular system, including the lymph, and all body fluids in the humoral system, reacts to water stress like a single organ system [1] at mesoscopic scales [194–196,307,308] in a quantum coherent manner.

Exogenous surfactant-induced interfacial surface tension, *i.e.*, “water stress,” is the biophysical basis [1–3] for the generalized Sanarelli-Shwartzman phenomenon, generalized thrombohemorrhagic

phenomena, the nonspecific generalized stress adaptation syndrome, the systemic inflammatory response syndrome, immune cell activation, macropinocytosis [73,304–306], vesiculation [77], adhesion [63,64,78], engulfment [45,46,256], envelopment [309], fusion [74,77,78,172,309–311], podokinesis [312–315], transcellular diapedesis [316] and nutritive endocytosis [317–320]. These highly-stereotyped supramolecular (mesoscopic), quantum coherent, biological processes are examples of the biophysical properties which motivate homeopathy.

ZP-lowering immediately lessens microvascular perfusion and increases interfacial water stress throughout the entire vascular system, especially in the terminal watershed vascular distributions. This explains sudden death from snake bites [321,322], vaccines [323–333], and cocaine [215], in otherwise healthy people, as examples. Depending on their surfactant property and their position within the Hofmeister series, environmental biological or chemical intoxicants of virtually any type can provide the EIWS to induce SDS. Certain dietary deficiencies, e.g., sulfur and zinc, and lack of adequate sunlight are likely to predispose to SDS. Bio-sulfate deficiency, in particular, is very likely to lower the threshold for an exogenous interfacial water “stressor” to induce the branching (avalanche-like) chain of reactions we have referred to as SDS. Our basal endogenous interfacial water tone is likely to be closely-related to bio-sulfate levels. Inorganic sulfate and the bio-sulfates—Ch-S, sulfated GAGs, and sulfated glycolipids—play an essential role in preserving and maintaining our ZP. It is appropriate that they be strongly considered for use as biomarkers of disease, including autoimmune, neurodegenerative, and oncologic disease [334]. Both bio-sulfate levels and measurement of EIWS may ultimately prove to be useful in diagnosing Shoenfeld’s syndrome [335], the autoimmune (autoinflammatory) syndrome induced by adjuvant (ASIA). Sunlight exposure to the skin is essential to the maintenance of the supply of Ch-S to the blood system and to the tissues, mediated by eNOS.

#### 4. Conclusions

We have reviewed the colloid and interface science literature as a basis for proposing a new hypothesis as to the cause of the Sudden Death Syndrome. We have defined the concept of surfactant-induced interfacial water stress and conclude that the initial events in the inflammatory cascade are purely biophysical. We have detailed the role of the bio-sulfates in maintaining cell membrane function and the role of endothelial Nitric Oxide Synthase-derived Nitric Oxide in acute shock and the Sudden Death Syndrome.

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