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Review Article

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A Novel Approach to Tissue Damage: Status of the Parenchyma? Degrees of Ischemia with Re-Perfusion Injury? Systemic Status of the Micro-Vasculature? Preliminary Findings Support the Importance of All Three

Michael F Angel*

University of Georgia, Department of Philosophy Graduate student, unassigned, USA

***Corresponding author:** Michael F Angel, University of Georgia, Department of Philosophy Graduate student, unassigned, USA.

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Abstract

This communication is a short summation of work of my work clinically and in the laboratories of multiple institutions for over forty years. A recent search of the literature [basic science/ clinical] and review analyses are reported. I posit there are enough necessary data to support this hypothesis. It is my hope; this paper may stimulate others to pursue further studies. I realize these studies to be consequential, require a multi-disciplinary approach. Finally, although it is anecdotal, I report my clinical course during the Covid era, which manifested all 3.

Introduction

The issue of tissue ischemia and tissue necrosis. How tissue, organs and whole organisms died has been somewhat mysterious. Ancient and more recent concepts such as 'humors', medicinal herbs, 'blood-letting 'arose [1,2]. Once anatomy was slowly evolving over several centuries, it became obvious as Aristotle posited in antiquity that, every living thing has form [anatomy, the modern term] and and function [physiology, the modern term] [3]. J. Muller established an early department of physiology with his book, "Handbuch der Physiologie des Menschen" published in 1830's [4]. Subsequently, Virchow in 1858, conceived the cell as the focal point of pathological changes [5] This replaced previous nonscientific ideas. Multiple authors present up to date data on this topic [6-8]. They document multiple pathways: inflammatory response to damage, apoptosis. autophagic cell death, lysosomal cell death etc. Our work in this field commences in the 1980's. We were deeply influenced by other renown faculty at The University of Pittsburgh at the time: Starzl [9], Safar [10], Maroon [11] who were concerned with these issues. Our work first started with the dorsal rat flap, which we standardized and concluded is a model for incomplete [partial] ischemia [12-15]. We found involvement of oxygen derived free radicals as the prime etiological mechanism. Hematomas under partially ischemic, lead to tissue necrosis by the same mechanism [16,17]. We published a review/hypothesis of these issues [18]. We

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then studied pedicle rat flaps under various conditions. Necrosis is caused by the type of ischemi, and the presence of re-perfusion injury [19-20]. We then studied various methods to improve tissue survival: vasodilation agents [21,22]; use of DMSO [23], and Fluosol [24], which was used experimentally in transplant surgery. Other transplantation strategies for liver, were studied by us: cold/ hyperbaric O2 storage [25], and the administration of L-NAME [26].

We studied prior elevation of skin flaps [27], flap delay [28] and effect of tissue ex-pansion on ischemic tolerance- it improves it [29,30]. This allowed us to construct expanded flaps for patients [31,32]. Arteriovenous fistulae surgically we created were useful for several reasons [33]. We found the ideal hematocrit for highest blood flow ie balancing oxygen carrying capacity vs viscosity is 30 [34]. We studied the role of free radicals and eicosonoid pathway species in flap surgery [35-38]. We studied these issues in muscle [39,40], and venous flaps, often used in hand surgery [41,42]. We then studied compressed optic nerves and peripheral nerves [43,44]. Knowing from other literature that diabetes mellitus is a cause of increased oxidant stress, sought methods to further study this issue [45-47]. We had previously been interested in venous insufficiency, wondering why it often resulted in ulceration, while this was less common in lymphedema. We proposed possible mechanisms [48]. Biopsies in patients confirmed our suspicions [49] which has been confirmed years later. We next studied patients with Carpal Tunnel Syndrome [CTS], sampling tenosynovium obtained at time of surgery, and obtaining blood for markers of inflammation [50]. We found elevated free radical markers both in the tissue, but interestingly in blood, suggesting that CTS has a systemic component! Molecular markers found elevated are those, others have subsequently found involved. Researchers at the University of Michigan, found similar results in bone [51]. This leads to the next issue -deeper analysis of the microvascular structure and function.

Aspects of Vascular Structure and Function

Arteries, which carry blood from the heart to the rest of the body are of 2 types. Elastic arteries, closest to the heart have fibers, which catch blood and absorb this force [52]. Muscular arteries carry blood to the microvascular system. Their anatomy is: tunic intima, tunica media, and tunica externa. The intima has endo-thelial cells, and a network of connective and elastic tissue [53]. Intact intima is crucial to maintain normal blood flow. The endothelial cells are present with a small amount: fibrocytes, smooth muscle, elastic fibers, collagen in a sub-endothelial stroma [54]. Normal blood flow supports an environment that inhibits

the formation of clots. If the underlying stroma is exposed, chemical mediators and cellular response can lead to thrombus formation [55,56]. This has several ramifications. One, this affects flow to tissue, whatever type, when surgery is commenced. I discuss above some of these issues. Two, this opens a second area, which is germane to most physicians especially cardiologists, and primary care - atherosclerosis. Montinari presents a recent article, concerning this over the centuries [56m]. She documents this story from antiquity, which has had many 'innovations' [my word, because these can be described as 3 steps forward/ 2 steps back]. The state of the knowledge from 1980 -recently routinely included avoiding fats, butter, eggs and milk was discouraged, use of statins etc. The Johns Hopkins University issued new guidelines, very different only seven months ago [57]. These include early screening, particularly for high genetic risk people, but most telling is the conclusion that '80-90%' of disease has at least some life style choices which can be modified. This is a 'first and foundational' approach. An appreciation of inflammation being a prime cause whether from autoimmune disease or diabetes mellitus, which has an immune effect. There are also calculations based on biological age, which has substantial validity and reliability from decades of study. This is praise-worthy, but a major issue, I have is that this alone is insufficient. Biological 'clocks' are also crucial. This is an assessment of the age of your cells. There are several approaches, most recent being telomere length [58], and subsequently from work at MIT, that gene function over time gets blocked by methyl groups [59]. They found 'typical' 40 ,50 ,60 …year olds had a pattern, which a swab of buccal mucosa could detect. I personally did the swab, and with 45+ history of taking supplements, I found my cells were decades younger. A related topic is the renin/ angiotensin system summarized in 2025 [60]. This system has been studied for decades. Several yrs ago receptor blockers were developed ie losartan, which I was prescribed by my LMD. I have had excellent control, without side effects. Of note, during the recent Covid episode [virus / 'vaccine', which is a construct allowing the transportation and incorporation of genetic material to foster cellular production of factors to combat Covid. Developers of this process, received the Nobel Prize in 2023 [61]. It now opens the door to begin treating a wide range of disease including cancer [62]. A personal observation of mine was after I had Covid [evident by antibody tests, still positive 2 1/2 yrs later], I noted several things: 1/2 of my tablet was sufficient to control BP [safe to assume my receptor was altered]; my allergy pro-file changed; I, despite being able to adequately function, had a tachycardia of 90 bpm, for 6 mo, presumably caused by microvascular dysfunction. The mechanism of its resolution is, unclear because of multiple factors. Time to resolve is obviously important; however, my recipe of supplements and use of natokinase [to lyse clots in micro-arterial systems [63], might have also played a role. Welldesigned studies are needed to resolve this issue.

Extravascular Space

It is well established that between the smallest arteries and veins, there is leakage of fluid and cells documented by fluorecein [64], and devices such as the spy [65]. Decades ago, we hypothesized a relationship between free radicals [major action vasoconstriction] and the eicosinoid pathways, affecting leakage. This work, as noted above, has been confirmed. However, things are much more complex now, as stated multiple times, throughout this paper. Nonetheless, several statements appear reason able.

A Novel Means of Assessing Physiological Damage

This classification is based on work summarized above. It has 3 parts. One, treat the parenchyma i.e. organs vary in multiple ways. Thus, there are tx protocols for stroke [66], Myocardial dysfunction [67], kidney failure [68], compartment syndrome [69] etc. Two, treat according to the degree of ischemia and +/- presence of the reperfusion injury [70,71]. Three, treat the extravascular space [72-75]. Note none of these reviews use, measures we have found useful. This is expected in these complex times. These are all excellent articles, but none of the authors are plastic surgeons, and presumably the audience has little to none representation. To repeat, this is a 3prong attack!. There is now an appreciation that patient care is now 2 sided- sx oriented i.e. standard allopathic medicine [76] and maintain wellness i.e. anti-aging medicine [77], functional medicine [78]. A summation and assorted thoughts are next.

Summation of this Brief Communication

One, when comparing chemical/ molecular mechanisms to physical factors, the physical ones are often more important. Two, when treating a condition, there are often 2 regimes, and as in 1, the local choice is often the better course. Two examples are: the spraying of a nasal spray to kill the Covid virus [79]; topical treatment of skin diseases [80] and treatment of oral /oropharynx in dentistry [81]. The most important message of this paper, is that practicing medicine and medical research, is the most complex it has ever been, and this trend will continue into the foreseeable future. Thus stated, several principles are: 1 medicine/surgery and re-search are noble and important professions. One must try to maintain exemplary character and behavior realizing that we sometimes fail, but truly take responsibility for these actions and ask forgiveness. Realize, no one knows everything, and find people both professionally and personally who are trustworthy, and have comple-mentary skills. Two, life is a series of journeys. Cavafy, a renown Greek poet from early twentieth century in his poem, states the journey must be savored - be observant, respectful and learn from other. Even if Ithaca does not exist, is irrelevant, because life is a series of journeys [82].

Acknowledgement

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Conflict of Interest

None.

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