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Special Issue on Professor John M. Tarbell's Contribution to Cardiovascular Engineering

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Commentary

Special Issue on Professor John M. Tarbell's Contribution to Cardiovascular Engineering

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Professor John M. Tarbell's contributions to the biomedical engineering community have been substantial through service, education, and research. These contributions have spanned approximately 45 years with his research efforts impactful in areas of mechanical heart valves, artificial hearts, cardiovascular fluid mechanics, vascular permeability, and mechanobiology. Professor Tarbell's legacy goes well beyond just his own research efforts, and this special issue of Cardiovascular Engineering and Technology celebrates his impact through collaborators, trainees, and close colleagues. To celebrate the lifetime achievement of Professor Tarbell, his former trainees, collaborators and colleagues have contributed ten papers including two review papers on the areas of artificial heart, heart valves, glycocalyx, and endothelial permeability to macromolecules and therapeutics in this Special Issue of Cardiovascular Engineering and Technology. Here, we first introduce each paper and Professor Tarbell reflects on his professional success, which continues today.

The papers collected in this Special Edition are grouped into the areas of (1) mechanical heart valve, artificial hearts, and heart valves, (2) the glycocalyx, (3) endothelial permeability, and (4) endothelial gene and drug delivery.

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MANNING *ET AL.*[25] JOHN M. TARBELL: ARTIFICIAL HEART AND MECHANICAL HEART VALVE RESEARCH CONTRIBUTIONS

Keefe Manning, Professor at the Pennsylvania State University (Penn State), was a former postdoctoral fellow in John Tarbell's lab at Penn State. In this Special Issue, he and his colleagues including Gerson Rosenberg, Tarbell's former student at Penn State, review Professor Tarbell's contributions to the artificial heart and mechanical heart valve research at Penn State.[25] John Tarbell initially developed techniques to measure shear stress using hot-film anemometry. In collaboration with colleagues at Penn State Hershey Medical Center, John studied fluid mechanics of artificial heart and ventricular assist devices, which have provided crucial guidance for the pump development.

HOWSMAN AND SACKS.[17] ON VALVE INTERSTITIAL CELL SIGNALING: THE LINK BETWEEN MULTISCALE MECHANICS AND MECHANOBIOLOGY

Michael Sacks, Professor at the University of Texas Austin, is a long-time colleague of John Tarbell in the field of heart valve mechanics. In this Special Issue, Sacks and Daniel P. Howsmon provide an in-depth review on the current understanding in vascular mechanobiology.[17] In an attempt to provide a better understanding by which heart valves function under the mechanically demanding environment, they propose mechanistic mathematical modeling between the mechanoresponses of vascular interstitial cells. This should be helpful in identification of drug targets for treating valve disease.

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SALIM *ET AL.*[30] TRANSCATHETER AORTIC VALVE THROMBOGENESIS: A FOREIGN MATERIALS PERSPECTIVE

Ajit P. Yoganathan, Professor at Georgia Institute of Technology, is a long-standing close colleague of John Tarbell in the field of fluid mechanics of heart valves. In this Special Issue, Yoganathan and colleagues report their work on the thrombogenic potential of transcatheter aortic valves (TAV).[30] Aortic stenosis is primarily caused by aortic valve fibrosis and calcification. Since there are no drugs available to treat aortic stenosis, aortic valve replacement through either a surgical or transcatheter approach are the only options currently. Increasingly, minimally invasive transcatheter aortic valve replacement (TAVR) is used to treat aortic stenosis. Leaflet thrombosis is a major clinical complication associated with TAVR. However, despite its clinical importance, the mechanism by which thrombus formation in TAVs is not well understood. In this report, the Yoganathan team studies a mechanism using human blood and the SAPIEN XT valve. They show a lower thrombogenic potential of intact SAPIEN XT valves compared to the stent-with-skirt (leaflets removed from a SAPIEN XT valve), indicating the significance of blood–stent and blood–skirt interactions in TAV thrombosis.

WEINBAUM *ET AL.*[37] THE GLYCOCALYX AND ITS ROLE IN VASCULAR PHYSIOLOGY AND VASCULAR RELATED DISEASES

Professors Sheldon Weinbaum and Bingmei M. Fu are close colleagues at the City College of New York (CUNY), while Limary M Cancel is a former PhD student and current colleague of John Tarbell. In this Special Issue, Weinbaum, Cancel, and Fu joined with John Tarbell to review their common topic of interests on the glycocalyx.[37] They summarize the current knowledge on the role of endothelial glycocalyx in intercellular interactions and how it is implicated in atherosclerosis and cancer metastasis. The luminal surface of vascular endothelial cells are coated with glycocalyx, which is the hydrated gel-like structure. Glycocalyx is comprised of core membrane proteins syndecans, and glypicans, with their covalently bound glycosaminoglycans (heparin sulfate, chondroitin sulfate, and hyaluronic acid). In Part A of this paper, the authors provide a state-of-the art review on the function of glycocalyx in basic vascular physiology and vascular-related diseases. The paper discusses the Michel-Weinbaum glycocalyx model and its physiological ramifications. New insights into the role of glycocalyx in shear stress-induced release of nitric oxide is discussed. Major technical advances in structure and function of glycocalyx are also discussed. In part (B), they summarize the role of glycocalyx in cardiovascular diseases, aging, cancer, and infectious disease including Corona viruses and further discuss the potential drugs and therapeutic strategies to target glycocalyx and associated diseases.

MENSAH *ET AL.*[26] ENDOTHELIAL GLYCOCALYX-MEDIATED INTERCELLULAR INTERACTIONS: MECHANISMS AND IMPLICATIONS FOR ATHEROSCLEROSIS AND CANCER METASTASIS

Eno Ebong, Associate Professor at Northeastern University, was trained with John Tarbell as his postdoctoral fellow at CUNY. In this Special Issue, Ebong and her colleagues review the role of glycocalyx in atherosclerosis and cancer.[26] Degradation of the glycocalyx disrupts endothelial cell function and is implicated in the onset of diseases such as atherosclerosis and cancer. The paper discusses how glycocalyx regulates endothelial function by regulating intercellular interactions between endothelial cells with their neighboring endothelial cells and cancer cells. The role of a junctional protein such as Connexin 43 in interendothelial communication and the cell surface receptor E-selectin in endothelial-tumor cell interactions is discussed, and the potential of glycocalyx protection and regeneration as therapeutic strategies is also discussed.

DU *ET AL.*[10] ANISODAMINE HYDROBROMIDE PROTECTS GLYCOCALYX AND AGAINST THE LIPOPOLYSACCHARIDE-INDUCED INCREASES IN MICROVASCULAR ENDOTHELIAL LAYER PERMEABILITY AND NITRIC OXIDE PRODUCTION

Ye Zeng, Associate Professor at Sichuan University, received postdoctoral training in the Tarbell Lab at CUNY. In this Special Issue, Zeng and his team studies the role of an Anisodamine hydrobromide (Ani HBr) in protection of endothelial glycocalyx layer, which in turn preserves the barrier function and nitric oxide production.[10] Ani HBr is an active component of Sco*opolia tangutica* maxim and is used to improve microcirculation in patients with cardiovascular disease and sepsis, but its mechanism is still not well understood. Here, Zeng's team shows that treatment with ani HBr protects glycocalyx layer of a human cerebral microvascular endothelial line (hCMEC/D3) in response to the bacterial endotoxin lipopolysac-

charide. Ani HBr also protected endothelial permeability barrier and junctional integrity against the lipopolysaccharide challenge. This finding suggests a potential use of Ani HBr as a drug to protect the endothelial glycocalyx and associated diseases.

DULL *ET AL.*[11] THE GLYCOCALYX AND PRESSURE-DEPENDENT TRANSCELLULAR ALBUMIN TRANSPORT

Randy Dull, Professor of Anesthesiology at University of Arizona, received his Ph.D. under the co-mentorship of Professors John Tarbell and Ted Hollis at Penn State, before he received his M.D. In this Special Issue, Dull and colleague's studies examine the role of glycocalyx, nitric oxide, and reactive oxygen species on endothelial permeability to albumin in response to pressure.[11] Hydrostatic pressure is known to activate endothelial signaling pathways that modulate barrier function and vascular permeability. His team used rat lung microvascular endothelial cells to measure uptake and transcellular uptake of albumin in response to hydrostatic pressure. Using heparanase to disrupt glycocalyx, L-NAME to inhibit endothelial nitric oxide synthase (eNOS), and apocynin to chelate reactive oxygen species, his team demonstrates that heparan sulfate, a key component of glycocalyx, eNOS, and reactive oxygen species play important regulatory roles in uptake and transcellular transport of macromolecules across endothelial cells in response to pressure conditions. The physiological and clinical implications of this finding is discussed.

GHIM *ET AL.*[16] THE ROLE OF TRICELLULAR JUNCTIONS IN THE TRANSPORT OF MACROMOLECULES ACROSS ENDOTHELIUM

Peter Weinberg, Professor at the Imperial College London, is John's long-time colleague since they began collaborating at Imperial College during his sabbatical in the Colin Caro's Lab. In this Special Issue, Weinberg and colleagues review the transport of macromolecules across vascular endothelial cells with special emphasis on paracellular junctions.[16] Macromolecules such as those with the sizes of albumin and low density lipoproteins use either transcellular or paracellular routes to pass through vascular endothelial cells, but the detailed understanding on their relative importance of each route is unclear. In this study, the authors studied the role of endothelial tricellular junctions in paracellular permeability using human aortic endothelial cells, fluorescent Avidin binding to biotinylated gelatin matrix, and machine-learning aided image analyses. They also investigated the role of agonists (sphingosine-1-phoshate and thrombin) and shear stress on the tricellular pathway. Their results show the dominance of the tricellular junctions for the macromolecule transport in response to the agonists and shear stress.

ZHANG *ET AL.*[41] TRANSCELLULAR MODEL FOR NEUTRAL AND CHARGED NANOPARTICLES ACROSS AN *IN VITRO* BLOOD–BRAIN BARRIER

Bingmei M. Fu, Associate Professor at CUNY, is a close collaborator of Professor Tarbell. Blood–brain barrier (BBB) is critical in limiting the transfer of most blood borne molecules including toxins across the endothelium to the brain tissue. On the other hand, BBB is a significant hindrance in delivering drugs to treat brain disease. In this Special Issue,[41] Bingmei Fu and her colleagues investigated transcellular characteristics of various nanoparticles across brain endothelial cells to develop optimal drug delivery vehicles. Using the mouse brain microvascular endothelial cells (bEnd3 cells), they found that positively charged nanoparticles (20–100 nm diameter) show favorable transcellular permeability, due in part to the negative charge of the surface glycocalyx of the BBB. Their predictive model for nanoparticle size and charge should be helpful in developing optimal drug delivery strategy across BBB.

DOSTA *ET AL.*[9] DELIVERY OF SIRNA TO ENDOTHELIAL CELLS *IN VITRO* USING LYS/HIS OLIGOPEPTIDE-MODIFIED POLY(*B*-AMINO ESTER) NANOPARTICLE

Hanjoong Jo, Professor at Emory University and Georgia Tech, was co-mentored by Professors John Tarbell and Ted Hollis at Penn State. In this Special Issue, Jo and his colleagues report on poly(b-amino ester)s (pBAEs) nanoparticles that were used to deliver siRNAs (small inhibitory RNAs) to vascular endothelial cells *in vitro* and *in vivo*.[9] Endothelial cell dysfunction plays a critical role in atherosclerotic and pulmonary diseases and cancer. Here, the authors developed the lysine-/histidine-oligopeptide modified pBAE (C6-KH) nanoparticle carrying siRNAs, which was able to specifically knockdown ICAM2 in endothelial cells both in cultured mouse aortic endothelial cells *in vitro* and mouse artery *in vivo*. In addition, they found that C6-KH pBAEs nanoparticles can be used for tissue-selective delivery of siRNAs to

the aorta and lung, while avoiding the liver and heart. The tissue-selectivity may be used for targeted drug and gene therapies.

We hope you enjoy and appreciate Prof. Tarbell's reflection and his many contributions through this special issue. Personally, he is an amazing mentor and friend that has help shape our careers.

Sincerely,

Hanjoong Jo and Keefe Manning

FOREWORD

This special issue of CVET recognizing my career contributions to cardiovascular research has been organized by my good friends Ajit Yoganathan, Hanjoong Jo, and Keefe Manning. They asked me to write a brief introduction reflecting on my career, and I have decided to constrain my comments to research, not discussing teaching and administration, which were so important to me as well. I have included enough depth to allow me to recognize many important people who influenced me, but I have avoided an exhaustive review of my publications. I hope you enjoy the excellent papers in this special issue of CVET.

REFLECTIONS ON A RESEARCH CAREER: JOHN TARBELL

Like many of my generation who have had careers in Biomedical Engineering, my original training was not in BME. I obtained BS (Rutgers University), MS and PhD (University of Delaware) degrees in Chemical Engineering. I received strong training in fluid mechanics at Delaware and the first research that ultimately proved relevant to my career was my Masters thesis work "A Numerical Study of Fluid Flow and Heat Transfer in Helical Coils". That may not sound terribly relevant at first, but it introduced me to the complexity of flow that could be induced by the curved tube (artery) geometry, including secondary flows (Dean vortices) and the skewing of the axial velocity profile toward the outer wall where shear stresses at the wall are higher than at the inner wall. This ultimately turned out to be relevant to the role of fluid mechanics in atherosclerosis that is localized in the low shear stress regions of inner curvatures in blood vessels.

When I was recruited by Penn State University's Chemical Engineering Department as an Assistant Professor in 1976 my initial research projects were not related to biomedical engineering at all. My first 13 publications were non-biological and dealt with such topics as air pollution kinetics and the stability of chemical reactors.[31,27] My last non-biological publication actually appeared in 1993.[19] Fortunately during my early years at Penn State I received strong encouragement from my chemical engineering colleague, Jim Ultman who worked in the area of respiratory transport, to pursue my bioengineering interests. In those early years I knew that I had a passion for research and was eager to work on any interesting problem be it a chemical reactor or flow in the aorta.

My earliest attraction to biomedical engineering research was inspired by the classic paper by Colin Caro *et al.*[6] which I had encountered in my fluid mechanics studies as a graduate student. This paper put forth the "low shear stress theory of atherogenesis" based on observations of atherosclerotic plaque localization in animals and humans. It was at odds with the popular "high shear stress theory" introduced by Donald Fry.[15] The Caro *et al.* paper also contained an appendix with a mathematical model of mass transport to and from the artery wall. [6] My eyes were opened to the possibility that chemical engineering principles of fluid mechanics and mass transfer could be applied to elucidate a significant biomedical problem—atherosclerosis. I soon found out that there was a faculty member in the Physiology Dept. at Penn State (Ted Hollis) who was studying the effects of fluid shear stress on endothelial cells.[8] I began a collaboration with Ted that led to my first biomedical engineering publication[32] ("A Note on Wall Shear Stress in the Aorta").

My interest in atherogenesis continued to grow mainly from the fluid mechanics perspective. But I knew that I needed to understand cellular behavior, and I was very fortunate to be invited for my first sabbatical to the "Physiological Flow Studies Unit" (PFSU) at Imperial College, London directed by Colin Caro. Working closely with the late John Lever and Colin on *ex-vivo* experiments in rabbit carotid arteries we measured hydraulic conductivity in response to changes in albumin concentration[34] and shear stress.[22] These studies demonstrated shear dependent hydraulic conductivity of the artery wall and initiated my enduring interest in shear dependent transport properties of arteries. While at the PFSU I met a bright young PhD student in the lab, Peter Weinberg, a contributor to this volume, who has sustained a career studying arterial wall transport and the influence of fluid mechanics. Peter has been a valued colleague and one who has consistently challenged conventional wisdom in his field.

When I returned from London, I knew I wanted to study shear effects on endothelial transport, but it was clear to me that I could not pursue the animal experiments we had performed in London—they were just

too technically difficult. I thought cell culture experiments might be more accessible to an engineer. I was fortunate to co-mentor two physiology PhD students with Ted Hollis (Hanjoong Jo and Randy Dull) to initiate studies of shear dependent transport across endothelial cell monolayers *in vitro*. With Hanjoong, currently at Emory University School of Medicine and Georgia Tech BME and a Co-Editor of this special issue, we developed a parallel plate flow chamber with a permeable wall section and demonstrated shear dependent albumin permeability.[18] With Randy, currently at the University of Arizona School of Medicine and also a contributor, we were able to measure hydraulic conductivity *in vitro* and to demonstrate the existence of a "large pore" pathway for albumin consistent with *in vivo* studies.[12] Over subsequent years an additional 35 papers on endothelial transport have been published.

In parallel to my burgeoning interest in fluid mechanics and atherogenesis, I became aware that there was an artificial heart program on our campus at University Park. It was established in collaboration with the Penn State Medical School at Hershey where the program was founded by William S. Pierce (MD) in the early 1960s. An engineering arm of the team was established at University Park in the early 1970s under the direction of mechanical engineering professors John Brighton and Win Phillips. As I was renting Win Phillips' house during my first year at Penn State while he was on sabbatical, my interest in the program was peaked. A few years later both Win Phillips and John Brighton left Penn State and I joined the group along with the late David Geselowitz from electrical engineering.

I began to direct the fluid mechanics aspects of the program in the early 1980s. With the help of Kirk Shung, an ultrasound expert in BME, and Steve Deutsch, a laser-Doppler velocimetry and particle image velocimetry expert in the Naval Fluid Mechanics Lab at Penn State, we assembled the tools and expertise to begin examining flow fields within artificial heart ventricles.[33,1] This led to my association with Ajit Yoganathan, founding editor of CVET and a contributor to this special issue. Ajit has been a valued colleague and friend throughout my career. Under Ajit's influence my lab began to investigate the fluid mechanics of mechanical heart valves in artificial hearts. We studied turbulence in forward flow and regurgitant flow[2] and made our most original contributions in the area of cavitation that occurs when mechanical valve leaflets rebound from their occluders at closure.[21,39] Cavitation can cause valve material damage and blood damage and generate nuclei for dissolved gas bubble growth that may lead to emboli in the brain.[4] Ultimately we began to look at blood damage generated within the artificial heart and by flow through the valves. This marked the first introduction of biological measurements to the artificial heart lab and this was aided by John Frangos, who was a young colleague in Chemical Engineering at Penn State.[20] At the end of 2002 I left Penn State for a new position at The City College of New York and that brought my artificial heart research career to an end. Fortunately I had an outstanding post doc in the lab for my last 5 years at Penn State–Keefe Manning,[24] who is a co-Editor of this special issue. Keefe soon became an Assistant Professor of BME at Penn State and took over direction of the Artificial Heart Lab which he oversees to this day.

In 1998 I took my second sabbatical in Boston with Rakesh Jain at the Steele Laboratory affiliated with Massachusetts General Hospital at Harvard University. Rakesh and I were classmates at Delaware in Chemical Engineering and he had established a strong research program in cancer research and the tumor microenvironment. Using equipment I transported from my laboratory at Penn State, I studied the effect of VEGF on the permeability of endothelial monolayers, working closely with Lance Munn who continues to be my collaborator today.[7] During my stay, I became aware of the strong interstitial flow present in the microenvironment of solid tumors that is associated with leaky blood vessels induced by VEGF. Using theory we published in 1995 for interstitial flow in arteries,[36] we estimated significant fluid shear stress on cancer cells in tumors induced by interstitial flow. This led to a series of studies of the effect of interstitial flow on tumor cells suspended in 3-dimensional collagen gels. We observed that migration of highly metastatic cancer cell lines was enhanced by interstitial flow whereas non-metastatic cells were not affected by interstitial flow.[28] This led to the hypothesis that interstitial flow enhances metastasis, and in collaboration with Lance Munn, this was demonstrated in animal studies in 2016.[29]

Shelly Weinbaum, whom I had known for many years through our common interest in arterial wall transport, recruited me to join the new BME Department at City College as the Coulter Professor and Department Chair in 2003. My PhD student, Limary Cancel, a contributor to this issue, along with Jeff Garanich and Mike Dancu helped set up the new lab. Limary stayed with me after her PhD, became a post doc, and is now a research associate and critical partner in my lab. Soon after arriving at City College, I discovered that Shelly and I were both studying the endothelial surface glycocalyx layer—a glycan rich gel like structure coating cell surfaces. I had shown in 2003 that the glycocalyx was a mechanosensor and transducer responsible for flow dependent induction of ni-

tric oxide production that, among many other functions, is responsible for flow mediated vasodilation.[14] Shelly had shown that the glycocalyx was responsible for shear dependent remodeling of endothelial cells.[35] In 2007, Shelly and I along with Ed Damiano at Boston University published a highly cited review paper on the glycocalyx.[38] In this current issue, we teamed up with Limary Cancel and my City College BME colleague, Bingmei Fu, to present a new and exhaustive review of the glycocalyx.[37]

Most of my recent effort at City College has been focused on the glycocalyx. Two of my latest and most productive post docs who studied the glycocalyx while at City have moved on to academic positions and continue studying the glycocalyx. Eno Ebong, Associate Professor at Northeastern University and Ye Zeng, Associate Professor at Sichuan University have each contributed glycocalyx papers to this special issue. At City College, in collaboration with David Spray at Albert Einstein School of Medicine, Eno produced the first cryo-EM images of the glycocalyx that overcame the dehydration artifacts associated with conventional EM and showed the full extent of the layer.[13] In collaboration with Victor Rizzo at Temple University School of Medicine, Ye observed the motility of glypican 1, an important membrane bound heparan sulfate proteoglycan (HSPG) in the glycocalyx, as it moved on lipid rafts in response to fluid shear stress while the transmembrane HSPG syndecan 1 was stationary in the presence of shear stress.[40] More recently, along with PhD student Anne Marie Bartosch, we showed that glypican 1 is the upstream mechanosensor for shear-induced NO production that acts through the intermediary junction protein, PECAM 1.[3] And most recently, with post doc Marwa Mahmoud, we showed that endothelial substrate stiffness that is associated with hypertension and aging, leads to glycocalyx suppression and endothelial dysfunction being mediated by a loss of glypican 1.[23]

At the time of this writing my lab continues to work on substrate stiffness effects mediated by the glycocalyx with Marwa Mahmoud, methods to suppress cancer metastasis through glycocalyx modification with Limary Cancel, Heriberto Moran and Lance Munn, and transport properties of the blood–brain barrier associated with transcranial direct current stimulation in collaboration with Limary Cancel, Bingmei Fu and my neural engineering colleague, Marom Bikson.[5]

As I look back on my career, which I am pleased to say is not yet over, I realize that I have worked on many problems, some would say too many. Actually I gave up on several areas that interested me to try and provide more focus and depth to my endeavors. But in the end I couldn't resist the excitement of discovery that was afforded by the many areas of research I have continued to pursue. As the saying goes, "I did it my way", and I have no regrets.

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