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Foreword

Harry L. Goldsmith, Ph.D.

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In honor of Dr. Harry L. Goldsmith's 80th birthday, we present a collection of articles from his collaborators and colleagues to commemorate Harry's outstanding contributions to the field of Biorheology. On any particular day, bioengineers around the world may find themselves fortunate enough to peer through a microscope to observe molecular or cellular level phenomena manifested before their eyes. Such observations of single molecule mechanics or blood flows or cellular deformation remind us of the power of clever experimental design and rigorous theoretical constructs as well as the complex beauty of dynamical systems in nature. In this spirit, the investigations reported in this issue of the *Annals* entitled *Cellular Biorheology and Biomechanics* have followed down many of the research paths pioneered by Dr. Harry Goldsmith.

Harry Goldsmith, born May 11, 1928 in Nurnberg Germany, obtained his BA (1950), and B.Sc. (1951) from Oxford University and his PhD (1961) from McGill University where he maintained his entire research career for over 50 years. While at McGill, he worked closely with eminent hydrodynamicists and physiologists such as Stanley G. Mason. Theo G. M. van de Ven, and Mony M. Frojmovic. Rising to the rank of Full Professor in the Department of Medicine, Harry also served as the Director of the Division of Experimental Medicine from 1976 to 1995. Notable awards include the Landis Award of the American Microcirculatory Society (1984) and the Poiseuille Medal of the International Society of Biorheology (1984). He served as President of the International Society of Biorheology (1983–86) and President of the North American Society of Biorheology (1990–92) and continues to serve as the Editor-in-Chief of *Biorheology* (1994–present).

The flow of ideas and methodologies at work in the scientific investigations captured in panoramic view in this issue also is a measure of the breadth of Harry's continuing impact. When today's generation of scientists and engineers see certain images in talks and textbooks, it is easy forget that it was Harry who first obtained the data in the days before high-speed digital cameras and image processing software, off-the-shelf numerical packages, and lab-on-a-chip microfluidic devices.

MICRORHEOLOGY OF HUMAN BLOOD

Through frame by frame tracking (cinephotomicrographs!) of rigid discs, fluid droplets, hard spheres, red blood cells (RBC), rouleaux, platelets, and red blood cells, Harry helped define the microrheology of blood flow. RBC rotational dynamics and deformation, liquid droplet deformation, enhanced radial dispersion, inward migrational drift, blunted velocity profiles, two-body collisions, and doublet rotation became the tools to understand the microscopic forces on particles within flow. In a classic example, Harry investigated the migratory paths of rigid and deformable particles in viscous flow both when Reynolds numbers were low (negligible inertial effects), and at larger Reynolds number when inertial effects were significant.[5] These studies demonstrated the importance of RBC fluidity and migratory drift in controlling the radial distribution of both the more-deformable RBCs and less-deformable white blood cells (WBCs) in blood flow.

In this issue of the *Annals*, this attention to particle microphysics is reflected in papers on the hematocrit dependence of blood viscometry from the *Takeshi Karino* laboratory and large-scale computational simulation of deformable leukocytes from the *Michael*

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King laboratory. *Lance Munn* also provides a detailed discussion of blood cell interactions and segregation in flow.

DISTURBED FLOW AND VASCULAR DISEASE

By tracking individual cells within complex flows in flow expansions and arterial bifurcations, the resolution of fluid mechanics on the length scale of single cells was united with large-scale macroscopic hemodynamics. For example, in one of many publications with Takeshi Karino[7] on platelet deposition downstream of a sudden expansion, a stenosis analog, the enhanced accumulation of platelets on collagen within the recirculation zone was studied as a function of flow pulsatility, Reynold's number, and hematocrit. In other work, particle trajectories in 30°, 90°, and 150° T-junctions were visually striking with spiraling vortexes set up opposite the flow divider with well-defined flow separation and reattachment points, a site prone to early plaque formation (Fig. 1). This dynamical complexity was fully apparent well before its use for chaotic laminar mixing now exploited in microfluidic devices. In contrast, rather orderly streamlines were often found at the flow divider in many configurations, a region spared of early disease in coronary atherosclerosis but susceptible to cerebral aneurysm.

In understanding the geometric localization of boundary layer attachment, vortices, and reversing flows, endothelial function became an interest in the context of atherosclerotic plaque localization, intimal hyperplasia, and graft distal anastomotic hyperplasia. Research of flow on endothelial function, in laminar or disturbed flows, as well as large-scale simulation of oscillatory flow through flexible bifurcations is now common. In this issue, papers from the laboratories of *Peter F. Davies*, *Shu Chien*, *Scott L. Diamond*, and *Larry V. McIntire* provide coverage of topics in endothelial mechanobiology.

COLLISIONS OF ACTIVATED CELLS IN SHEARED SUSPENSIONS

In activated blood flow, platelets moving in faster streamlines will have collisions with platelets in slower streamlines. The rate of single cell consumption into aggregates can be measured in linear shear fields or parabolic shear fields. For aggregation in tube flow, Bell *et al.*[2] found that activated platelets are fabulously sticky, with about 3 of 10 collisions resulting in adhesion due to GPIIb/IIIa-fibrinogen cross-bridging.

Harry contributed to studies of cell and particle interaction under flow by developing two novel and clever experimental systems. In the first setup called the 'traveling microtube apparatus,'[9] cell suspensions were subject to laminar viscous flow through a glass tube using gravity feed between infusion and collecting reservoirs. The slide and reservoirs were mounted on a jig and attached to the vertically sliding platform of a hydraulically driven traveling microtube apparatus. The translational and rotational motion of doublets could be viewed in this system with a camera attached to a horizontally positioned microscope by moving the

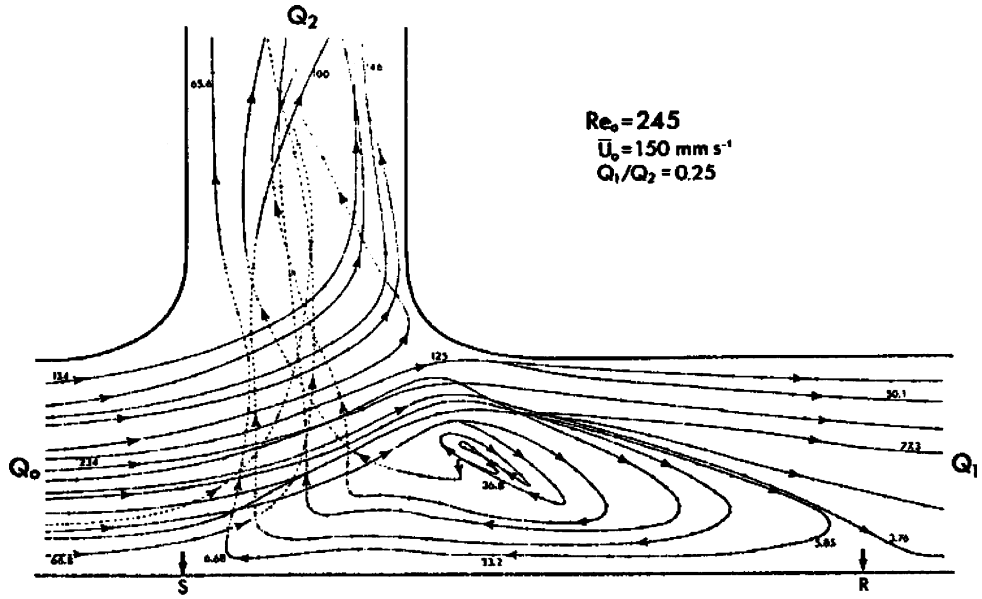

FIGURE 1. Particle paths in the rounded T-junction defining locations of boundary layer separation (S) and reattachment (R) adjacent to the flow divider. (Used with permission from Karino *et al.*[8]).

sliding platform upward at a velocity equal to that of the downward-flowing particles. In another novel experimental setup, Harry and colleagues developed a rheoscope which consisted of a counter-rotating transparent cone and plate viscometer mounted on the stage of an inverted microscope. In this system, the cone and plate were rotated with equal angular velocity in opposite directions such that a layer of zero translational velocity was located in the midplane between the cone and plate. Cell collisions and doublet could be viewed for extended periods of time at this midplane. Aggregation kinetics, collision efficiency, doublet lifetime, and period of rotation data could be collected using high-speed videomicrosopy.

To complement these experimental systems, existing hydrodynamic theory[1,3] was extended to derive explicit expressions for the nature and magnitude of normal and shear forces applied in the above experimental systems. These experiments and theory together provided some of the first estimates on the magnitude of hydrodynamic forces that prevail at the cellular level in various human vascular pathophysiologies during inflammation and thrombosis. The continual development of defined flow systems for blood diagnostic testing relies on controlling the frequency of cellular collisions and the forces applied upon adherent cells. In the current issue, *Mony Frojmovic* presents detailed arguments outlining the rationale supporting the application of flow devices and biorheology principles in the clinical setting to assess the drug and clinical outcome efficacy.

ADHESION: MICRORHEOLOGY AND MOLECULAR MECHANICS

With a long track record in single cell tracking and platelet aggregation, it was a natural extension of Harry's interests to begin quantification of the mechanics of receptor-mediated adhesion. A small story helps to capture the precision of Harry's experimental approach, the range of his understanding of molecular scale and macroscale phenomenon, and his attention to important problems. In a 1983 study of fixed, sphered RBC undergoing two-body collision, adhesion, and doublet rotation in the presence of anti-B antiserum,[6] Harry estimated the hydrodynamic force to break up a doublet formed at high antibody dilution to be $F_h = 6 \times 10^{-11}$ N and noted that this was appreciably less force than necessary to break a C–C bond. The published ''Discussion of the Paper'' captures a moment in time some 25 years ago when 60 pN (or 6 μdynes) became a first estimate of the force to break an antibody–antigen bond holding a doublet together in a flow field:

[R. M. Hochmuth (Duke University)]: I am interested in those forces of separation you had between your beads. Did they work out to be about 6×10^{-6} dynes? I cannot think in terms of nanonewtons, though.
[Goldsmith]: They were 6×10^{-11} N. You divide by 10^5 to get it back to dynes from Newtons.
[Hochmuth]: Yes...so it is 6×10^{-6} dynes.
[Goldsmith]: That is correct.
[Hochmuth]: ...What you really need is a force displacement relationship to get the free energy of adhesion or disaggregation.
[Goldsmith]: ...People have obtained equilibrium constants from which they can work out thermodynamic quantities, but they cannot work out the actual magnitude of the force of separation.

In the above discussion, it is no surprise that Harry knew the unit conversion and that he anticipated the hard work ahead in relating the dissociation constant measured by immunologists to the actual strength of a biological adhesion under hydrodynamic force loading. The ''microdynes'' of biorheology became the ''piconewtons'' of molecular biophysics. In fact, Harry had first published in 1981[4] the observation that ''forces of the order of 0.1 nN were required to break up these [antibody–antigen] linkages'' after completing a full characterization of the underlying DLVO interactions of latex spheres or fixed RBCs. The importance of background forces remains very significant because force loading regimes are often used today that can go down to the low pN ranges.

In the later part of his career, the Goldsmith lab would continue research on fibrinogen-mediated and von Willebrand factor (vWF)-mediated adhesion of platelets, L-selectin/PSGL-1 adhesion of neutrophils, as well as E-selectin and P-selectin mechanics. The exploration of receptor-mediated adhesion under mechanical loading continues to fascinate and challenge. In this issue, the topics of bond mechanics and adhesion are presented from the laboratories of: *Cheng Dong*, *Sriram Neelamegham*, *Scott Simon*, *David Tees*, and *Cheng Zhu*.

IN CLOSING

Overall, Harry Goldsmith advanced the use of many novel techniques in microrheology: the traveling microscope to image cells in tube flow, the counter-rotation plate flow to observe doublet collisions in a linear shear field, T-junctions and sudden expansions and vein valves for particle trajectory tracking. In today's world of interdisciplinary research, we can look to his early example of bridging colloidal hydrodynamics with the study of hemodynamics, platelet and neutrophil biology, and bond mechanics.

In a publication record spanning 50 years, Harry has shown himself to be a dedicated and meticulous scientist who consistently tackled and elucidated the most fundamental principle or phenomenon embedded in the study at hand. Throughout his career, he has been a kind mentor and collaborator to many younger scientists, eager to exchange ideas and insights. We are enriched by his warmth, his scholarship, and his many long lasting contributions to the fields of Biorheology, Physiology, and Biophysics.

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