In Memoriam: Colin Caro 1925–2022

Picture credit: Layton Thompson/Imperial College London

We write in remembrance of Colin Gerald Caro, one of the founders of bioengineering, a pioneer in the study of arterial fluid mechanics, an originator of the low-shear-stress theory of atherosclerosis, a scientist with outstanding insight and foresight, and a mentor to researchers around the world.

Colin was born in Durban, South Africa, in 1925. He read medicine at the University of Witwatersrand, graduating in 1950 after interruptions for service in the South African Navy (he assisted the surgeon aboard the frigate HMSAS Swale) and a degree in physiology. There followed a string of positions characteristic of the peripatetic life of a young physician-scientist—Baragwanath and Addington hospitals in South Africa, Canadian Red Cross and the Hammersmith hospitals in the UK, the State University of New York and the University of Pennsylvania in the U.S.—before he was appointed Lecturer at St Thomas's Hospital Medical School, London, in 1960.

A number of papers from these early years hint at his future path. One, with Donald A. McDonald, deals with pressure-flow relations in the pulmonary vasculature. Another concerns the dispersion of indicator flowing through simplified models of the circulation and will remind many of Colin at his happiest, in the lab decades later, injecting dye streams into transparent tubes of various tortured geometries precariously suspended from retort stands.

Of great significance was the establishment in 1966 of the Physiological Flow Studies Unit (PFSU) at Imperial College London; Colin was cofounder and its first Director. It was achieved with support from his friend, Professor (later Sir) James Lighthill FRS, one of the greatest mathematicians of the 20th century, who was then a Royal Society Research Professor at Imperial and himself investigating biological flows, and with enthusiasm from Sir Patrick Linstead, the Rector of the College. PFSU was one of the first biofluids groups anywhere in the world and it quickly grew to become an international powerhouse in the area.

Colin's foresight and political skills were matched by his fundraising and team-building abilities. The lack of an undergraduate teaching program meant that salaries and facilities had to be supported by external bodies. Over the years, Colin proved himself adept at obtaining grants from unorthodox sources, ranging from British Petroleum to the Worshipful Company of Clothworkers. The Charles Hayward Foundation helped with the 1976 construction of a suite of laboratories and offices on the roof of the Department of Aeronautics.

In 1966, no researchers were trained in bioengineering. Colin recruited an eclectic mix of talented mathematicians, physicists, engineers, biomedical researchers, and clinicians who shared his vision of a new, multidisciplinary approach but who had little if any previous experience of it. The initial group comprised Colin, Bob Schroter, Mike Sudlow, W. A. "Tony" Seed and Nigel Wood, and it grew with the appointments of Tim Pedley, Kim Parker, C. Peter Winlove, and M. John Lever. Importantly, interactions between the fundamental and applied researchers maintained both rigor and relevance, and the quality of the recruits led to excellence in new areas of research, outside of Colin's own developing interests, including respiratory airflow, tissue mechanics, physiological heat exchange, transport in connective tissues, the analysis of arterial pulse waves, and biofluid mathematics.

The Unit hosted sabbatical visits that triggered enthusiasm for physiological flows in such luminaries as Bob Nerem, Shelly Weinbaum, and John Tarbell. And its junior researchers from abroad—including Alain Tedgui, Takami Yamaguchi, and David Elad—were influential on returning to their own countries. Three of the applied mathematicians went on to become Heads of Department—at Leeds and Cambridge (Tim Pedley), Imperial College (Phil Hall), and UCL (Frank Smith)—a record of which any Mathematics department would be proud.

Less easy to document is the cohesiveness and zeal of a group with a mission to spread the word of the new approach. All biological systems obey physical and mathematical laws, of course, but it appears that some of these systems can best be understood from a physical and mathematical standpoint—an entirely different proposition that is now commonplace but was not so 50 years ago. Researchers around the world recall with nostalgia the depth and breadth of the tea-room discussions, wherein contributions from different disciplines came together to create a coherent whole. The success of the Unit led, over many years and through mergers with other pioneering Imperial groups, to the formation of the current Department of Bioengineering, one of the largest worldwide, with over 50 academic staff; cardiovascular biomechanics remains one of its foci. A key step in this process was the formation of the Center for Biological and Medical Systems in 1989 with Colin as its inaugural Director and, as a result of a generous donation, the construction in 1991 of the Sir Leon Bagrit Centre to house it.

Early research at PFSU, conducted by Bob Schroter and Mike Sudlow, concerned gas flow in airway bifurcations. Their experiments showed that near-wall velocities, and hence wall shear stresses, were higher on the flow divider walls of the bifurcation than on the outer, "lateral" walls. Shortly before, J.R.A. Mitchell and C.J. Schwartz had published *Arterial Disease*, a book documenting in exceptional detail the pattern of atherosclerosis in *postmortem* human arteries. The illustrations of branches showed that flow dividers were spared from disease. The fluid mechanical explanation given in *Arterial Disease*, derived from earlier work of McDonald, was that disease occurred in areas of high wall shear stress. It was clear to the PFSU team, fresh from their studies of airways, that this was wrong. Colin, Bob, and Jim Fitzgerald conducted a *postmortem* survey of their own and experimental studies of wall shear stress in a replica of an aorta. They found that atherosclerosis preferentially occurred in regions of low wall shear stress. The argument was presented in a series of publications, culminating in 1971 in a fifty-page paper in the Proceedings of the Royal Society. (The paper was introduced and contained comments by Sir James Lighthill.)

It took many years for the central thesis to become accepted. That reflects several factors. One was the work of Donald Fry, also a clinician investigating fluid mechanical explanations for the localization of arterial disease and working at around the same time at the National Institutes of Health in Bethesda. Fry, like Mitchell and Schwartz, suggested that atherosclerosis was triggered by high wall shear stress. However, there was an important difference. Fry employed the same fluid mechanical arguments as Colin and colleagues but used them to explain a different distribution of lesions, obtained in cholesterol-fed animals and familiar to researchers since the work of Anitschkow in the early 1900s.

A second factor was the lack of a satisfying mechanism. Fry's proposal was simple: high shear damaged the endothelium lining the inner surface of arteries, accelerating the ingress of cholesterol-carrying lipoproteins into the wall. The PFSU group, on the other hand, had to reconcile the occurrence of atherosclerosis with low wall permeability. Nevertheless, the low-shear hypothesis gradually became the consensus view, and the 1971 paper is a citation classic (almost 2000 citations at the time of writing). Important steps in its adoption were supportive studies of lesion distribution by the groups of Lars Walløe, Mort Friedman, Don Giddens, and Sy Glagov and, following the molecular biology revolution, the discovery of pro-atherogenic effects of low shear on endothelial gene and protein expression.

Subsequent research by Colin and his colleagues maintained the focus on the fundamentals of arterial mechanobiology in relation to disease. Transport properties of the arterial wall and their dependence on flow were the core topic for many years, aided by Bob Nerem's sabbatical and Colin's Royal Society visiting professorship at the Weitzman Institute, Israel; John Lever took over the lead in this area. The work examined mass transfer boundary layers and the effects of medial tone on the intimal accumulation of plasma macromolecules. It attempted to relate shear and transport in a way that was consistent with the low-shear hypothesis. Later work on the poor delivery of oxygen to deep layers of the arterial wall had the same aim.

There was also work on blood flow itself, including new ways of imaging it (with Charles "Chuck" Dumoulin, GE). A development with important implications was the concept that the nonplanarity of arteries influences the structure of secondary flows caused by their curvature, reducing areas of low shear. A collaboration with Spencer Sherwin, Denis Doorly, and others in the Department of Aeronautics provided expertise in numerical methods and led Colin to the concept that vascular stents with a helical geometry would, by promoting mixing, lead to better clinical outcomes. The resulting small-amplitude helical stent, a jewel-like nitinol structure produced by spinout Veryan Medical, gave promising results in a small study of pigs, and in experiments on arterio-venous fistulae and dialysis access grafts. Veryan is the name of a Cornish village where Colin's family maintained a second home, and the name of the spinout is an indication of his affection for the region.

Colin's influence was substantially enhanced by the 1978 publication of *The Mechanics of the Circulation*, a masterly textbook written with Tim Pedley, Bob Schroter, and Tony Seed. A feature of this widely read work was the exceptional clarity with which it explained the underlying physical laws, the product of three years of intensive brainstorming sessions. For that reason, it remains useful over forty years later; a second edition, with additional coauthor Kim Parker, was recently released.

A list of Colin's scientific achievements and publications explains only part of his influence. His insight, intuition, and foresight were highly valued. He chaired or sat on influential bodies, but his views were also sought less formally, at scientific meetings and in casual conversation. He spoke quietly—almost inaudibly—and his handwriting was illegible, as befits a physician, but those around him hung on his words and pored over his writing. He had gravitas and great presence, which undoubtedly aided his success, but he could also be mischievous. In the early days he was known for his furious driving around London of a Messerschmitt Kabinenroller (fortuitously also known as a Karo), a car with three wheels, two seats in tandem, a motorcycle engine, and not much else. In the same strain was his habit of throwing out oracular comments to see who could understand. An example is "Our grandparents were right," from which one was supposed to infer that they recommended a walk after dinner and that this increased blood flows to the legs at the expense of the stomach, thus reducing flow separation on the aortic wall opposite the celiac artery branch.

Above all, there was his constant enthusiasm and engagement. When he arrived in the Unit one morning, having cycled in across Putney Bridge, and announced that the empty crisp packets and other flotsam accumulated on the inner bend of the Thames and not the outer, nobody was surprised. It was expected of him. (Characteristically, the idea for the helical stent derived from observing how the flushing of his lavatory bowl was modified by a cake of soap hanging from the rim.) That intellectual curiosity drove him ever on. Retirement in 1991 was but a minor hiccup in his scientific journey. He retained an emeritus position and came to Imperial almost every day until the start of the pandemic 28 years later. He was still working on new ideas only weeks before his passing. His first and last papers are separated by sixty years; it was an extraordinary run. We honor and salute our teacher and friend.

Recognitions of Colin's achievements are too numerous to provide an exhaustive list. They include honorary degrees from London (2003), Paris (2005), and Witwatersrand (2010); an Invited Professorship at Tokyo Women's Medical College (First Awardee, 1981); Inaugural Member, World Council for Biomechanics (1990); Foreign Fellowship of the American Institute of Medical and Biological Engineering (Initial Awardee, 1994); Founding Fellowship of the International Academy of Medical and Biological Engineering (2000); the Arthur Guyton Award from the International Society of Cardiovascular Medicine and Science (2003); Outstanding Engineer at the Engineer Technology and Innovation Awards (2007); and Annual Harveian Lecturer at the Harveian Society of London (2011).

Colin was married to Rachel Alice Caro, an architect, for 57 years, until she died in 2013. He later married Marilyn Evans, who had worked at PFSU. Both were known and loved by Unit staff and students, whom they supported and nurtured. Colin is survived by a son and daughter from his first marriage, and their children and grandchildren.

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