BIOGRAPHICAL MEMOIRS

Charles T. Esmon

April 3, 1947–May 1, 2026
Elected to the NAS, 2002

A Biographical Memoir by Jun Xu, Alireza R. Rezaie, Florea Lupu, and Lijun Xia

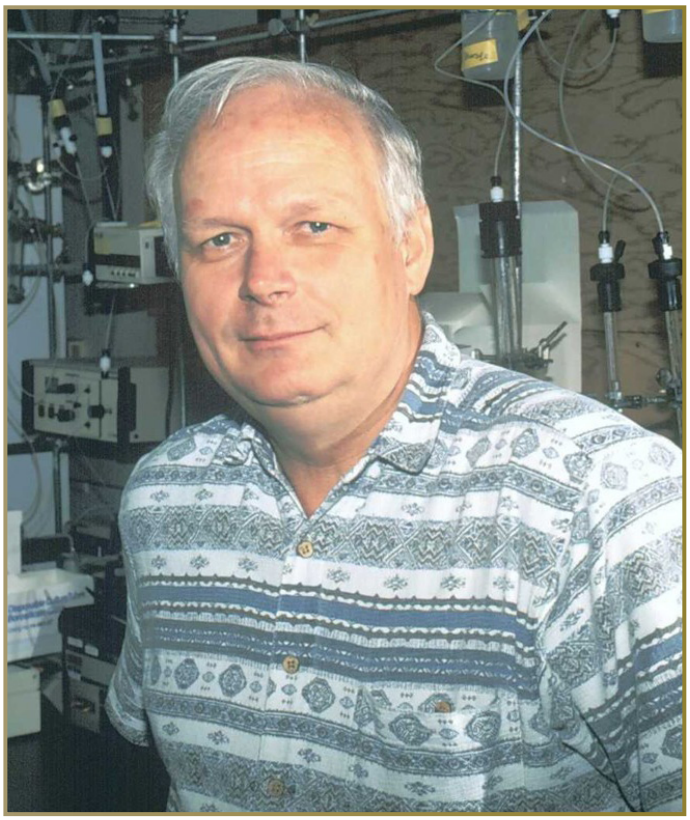

Figure 1 Charles T. Esmon. *Photo from the OMRF archives.*

Charles T. "Chuck" Esmon was a pioneering biochemist whose discoveries fundamentally transformed modern understanding of coagulation, thrombosis, inflammation, and endothelial biology. Over a scientific career spanning more than four decades, Esmon reshaped concepts in vascular biology by establishing the protein C pathway as a central endogenous regulator linking coagulation, inflammation, innate immunity, and host defense. His work revealed that the vascular endothelium actively governs hemostatic and inflammatory balance and led to therapies for sepsis, hereditary thrombophilia, and, more recently, bleeding disorders such as hemophilia.

Early Life, Education, and Early Career

Chuck Esmon was born in Centralia, Illinois, on April 3, 1947, to Myrtle Edmison Esmon and Noel Esmon, a farming family. He often described himself simply as a "country boy." He received a Bachelor of Science degree in chemistry from the University of Illinois in 1969 and a Ph.D. in biochemistry, under Craig Jackson, from Washington University in St. Louis in 1973. As a graduate student, Chuck and Whyte Owen, a postdoctoral fellow in the Jackson lab, made an enormous contribution to understanding the mechanism of the prothrombinase reaction.[1] While at Washington, Chuck also met Naomi Block, then a fellow graduate student. Chuck later joked that one reason Naomi initially noticed him was because, as a graduate student, he owned a television. Naomi became his lifelong partner in life, marriage, and scientific collaboration. After postdoctoral training at the University of Wisconsin, Chuck moved to Oklahoma in 1976 to take a position as an assistant professor at the University of Oklahoma Health Sciences Center. In 1982, Chuck and Naomi Esmon moved their laboratory to the adjacent Oklahoma Medical Research Foundation (OMRF), where Chuck spent the remainder of his career and established one of the world's leading programs in cardiovascular biology research.

Groundbreaking Research

At OMRF, Chuck's research focused on protein C, a vitamin K-dependent plasma protein whose physiological importance was poorly understood at the time. The work

initially faced considerable skepticism. As Chuck later recalled, some reviewers dismissed the project as merely "studying the appendix of the coagulation system." Nevertheless, through a series of elegant biochemical and cellular studies, he demonstrated that activated protein C (APC) is a major endogenous anticoagulant that selectively inactivates factors Va and VIIIa, thereby suppressing thrombin generation and limiting coagulation.[2,3] These studies helped establish the protein C pathway as one of the body's principal physiological mechanisms for limiting excessive coagulation.

At the time, thrombin was viewed almost exclusively as a procoagulant enzyme responsible for converting fibrinogen into fibrin and promoting clot formation within the circulation. Chuck reasoned that such a powerful procoagulant system would likely require an equally important endogenous negative regulatory mechanism to prevent uncontrolled thrombosis. Earlier observations had suggested that thrombin could also bind to the endothelial surface, although the physiological significance and underlying mechanism remained unclear. Chuck therefore hypothesized that endothelial cells might contain the critical machinery required for protein C activation and proposed the then-unconventional idea that thrombin could function not only as a procoagulant enzyme but also as a protein C activator. His work on protein C advanced rapidly through a collaboration with Whyte Owen, his former laboratory colleague at the University of Iowa. Using an elegant Langendorff rabbit heart preparation, Chuck and Whyte infused thrombin and protein C through the coronary circulation and collected blood from the coronary sinus draining the endothelial surface of the heart.[4,5] This experiment demonstrated that thrombin formed a complex with a previously unrecognized receptor on endothelial cells, profoundly altering thrombin's biological properties.[6-9]

This endothelial receptor was later named thrombomodulin.[10] Chuck's studies showed that when thrombin binds thrombomodulin, its procoagulant activity toward fibrinogen is suppressed and the enzyme instead becomes a highly efficient activator of protein C. Activated protein C, together with its cofactor protein S, then selectively inactivates factors Va and VIIIa, thereby limiting further thrombin generation through a powerful negative feedback mechanism. The discovery was especially important because it localized a major endogenous anticoagulant pathway directly to the endothelial surface.

Thrombomodulin's discovery fundamentally reshaped vascular biology and coagulation science. Before this work, coagulation pathways were viewed largely as plasma-based enzymatic cascades. Chuck's work demonstrated instead that the vascular endothelium is not simply a passive barrier separating blood from tissue, but an active organ that dynamically regulates hemostatic balance through thrombomodulin, protein C, protein S, and, later, the endothelial protein C receptor. Equally transformative was the realization that thrombin itself could function as either a procoagulant enzyme or an anticoagulant regulator, depending on its molecular context. These findings established an entirely new conceptual framework linking endothelial biology, coagulation, inflammation, and vascular homeostasis.

Chuck later discovered and characterized the endothelial protein C receptor (EPCR),[11,12] which greatly enhances protein C activation on the endothelial surface and also enables activated protein C to exert anti-inflammatory and cytoprotective effects.[13] Reflecting on these discoveries years later, Chuck wrote that scientific advances often begin with experimental findings "that simply fail to be explained by existing theories." This willingness to pursue unexplained observations became a defining feature of his scientific style.

Chuck was also among the first investigators to establish the intimate relationship between coagulation and inflammation. His studies demonstrated that inflammatory cytokines suppress endogenous anticoagulant pathways, increase tissue factor expression, and inhibit fibrinolysis, thereby creating a profoundly prothrombotic state. Conversely, APC was shown to possess potent anti-inflammatory and cytoprotective activities. These findings helped define the modern concept that coagulation and innate immunity are deeply interconnected biological systems.

These discoveries had especially profound implications for sepsis and disseminated intravascular coagulation (DIC). Working closely with Fletcher Taylor and others, Chuck demonstrated in primate and rodent models that impairment of the protein C pathway contributes directly to the lethal coagulopathy and organ failure of severe infection. His work showed that restoration of APC signaling could prevent the coagulopathic and lethal effects of *Escherichia coli* sepsis, fundamentally reshaping scientific understanding of endothelial dysfunction in critical illness and contributing to the development of APC-based therapies for severe sepsis. The translational impact of his discoveries was exceptional: Ceprotin remains an important therapy for severe congenital protein C deficiency, and recombinant APC, marketed as Xigris, represented one of the earliest successful efforts to translate fundamental vascular biology into a treatment for severe sepsis.

Later in his career, Chuck helped identify extracellular histones as major mediators of endothelial injury, thrombosis, and lethality in sepsis. His group demonstrated that APC can cleave histones proteolytically and reduce their cytotoxicity, revealing a previously unrecognized protective mechanism of the protein C pathway and advancing emerging concepts linking thrombosis, innate immunity, and sterile inflammation.[14,15]

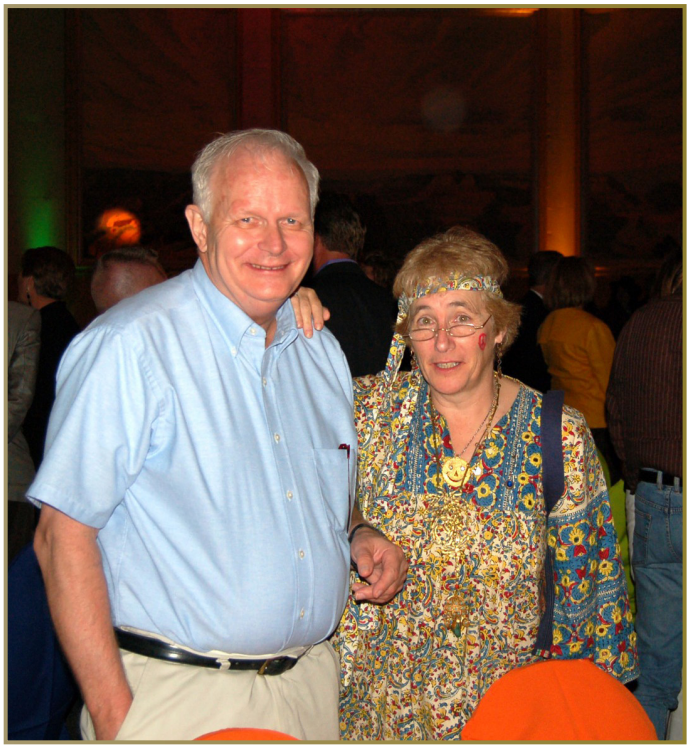

Figure 2 Chuck and Naomi Esmon at an OMRF party in 2016. *Photo from the OMRF archives.*

Retirement and Later Years and Honors

Although Chuck formally retired in 2019, he remained deeply engaged in science. In the final years of his career, he became actively involved in the development of a novel "rebalancing" therapeutic strategy for bleeding disorders based on anti-activated protein C antibodies originally generated in his laboratory. The concept, which partially inhibits endogenous anticoagulant pathways to restore hemostatic balance in hemophilia and related disorders, represented yet another example of Chuck's ability to rethink coagulation biology in fundamentally new ways. The therapy is currently undergoing advanced clinical development for hemophilia A and B, with or without inhibitors, as well as for factor VII deficiency and von Willebrand disease. Phase II clinical trials in China and the United States have been nearly completed, with phase III studies in preparation. Much of this work has been advanced by former trainees from Esmon's laboratory, extending the scientific lineage he cultivated over decades. Remarkably, he remained actively involved in the project until the final week of his life.

Chuck's scientific accomplishments earned many of the highest distinctions in biomedical research. In 1988, he became the first scientist outside a university to be named an Investigator of the Howard Hughes Medical Institute, a position he held for twenty-five years. He was elected to the National Academy of Sciences in 2002. He received numerous honors, including the National Institutes of Health MERIT Award, the American Heart Association Basic Research Prize, the Robert P. Grant Medal of the International Society on Thrombosis and Haemostasis, and the E. Donnall Thomas Lecture and Prize from the American Society of Hematology.

Chuck was remarkably modest, consistently rigorous, and intellectually generous. Fletcher Taylor, his longtime collaborator, once noted, "He thinks and writes in paragraphs, not sentences." Rodger McEver, another longtime colleague, remarked, "He was a remarkably creative scientist. He had that rare 'big-picture' ability to envision how the molecular processes that he defined so elegantly would influence both health and disease."

Those who trained in his laboratory remember an environment of careful thought, independence, and scientific honesty. Chuck encouraged young investigators to pursue difficult mechanistic questions, especially those whose importance was not yet clear. Equally remarkable was the extraordinary loyalty of the people who worked with him. Several laboratory technicians remained with Esmon for more than two decades, dedicating much of their professional lives to the scientific program he built. Their relationships extended far beyond the laboratory bench. Even after his retirement, some continued to support him personally and professionally, reflecting the deep bonds and mutual trust that characterized his laboratory. Over time, several longtime laboratory technicians became, in many respects, family to Chuck and Naomi. During his final hospitalization, Chuck was surrounded by them and by former trainees who had shared much of their lives with him. In many respects, his laboratory became his extended family.

Outside the laboratory, Chuck and Naomi shared a love of travel, scuba diving, skiing, boating, and their dogs. They traveled repeatedly to Fiji. Chuck maintained elaborate saltwater aquariums filled with many of the corals and tropical fish he encountered on his dives. Chuck and Naomi especially cherished time spent at Keystone Lake in Oklahoma, where they kept a houseboat and frequently welcomed friends, trainees, and laboratory members into a close-knit community that extended far beyond science. Naomi's death in the winter of 2025 deeply affected Chuck. Around that time, he expressed the wish that his ashes be scattered at Keystone Lake, a place associated with many of their happiest memories together.

Chuck Esmon's work fundamentally reshaped modern concepts of coagulation and vascular biology by revealing that the vascular endothelium is an active anticoagulant and anti-inflammatory organ and that coagulation pathways are deeply integrated with inflammation. From defining the protein C anticoagulant pathway to enabling next-generation

rebalancing therapies for bleeding disorders, his scientific legacy continues to evolve and to improve human health.

Chuck died on May 1, 2026, at the age of seventy-nine. His legacy lives on in former laboratory members and trainees, colleagues, collaborators, family, and friends whose scientific and personal lives were profoundly shaped by his mentorship, friendship, and example.

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