BIOGRAPHICAL MEMOIRS

Earl Warren Davie

October 25, 1927–June 6, 2020
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A Biographical Memoir by Dominic W. Chung and José A. López

Figure 1 Earl W. Davie.

Earl W. Davie is renowned for his ground-breaking research on the mechanism of blood coagulation. The so-called "Waterfall Sequence for Intrinsic Blood Clotting," proposed in 1964 by Davie and his collaborator Oscar D. Ratnoff, provided pivotal insight into the molecular basis of fibrin clot formation and had a profound impact on the development of diagnostic tests and therapies for bleeding disorders. Earl published more than 235 research papers and book chapters and received numerous accolades for his research accomplishments.

The Early Years

Earl was born in Tacoma, Washington, on October 25, 1927, but grew up in Alder, a very small town along the shore of Alder Lake in the shadow of Mount Rainier. Earl's father, Charles, was the operator of the Alder Dam power station. Earl attended the public high school in nearby Eatonville. In addition to his scholastic excellence, Earl was an all-round athlete and, at six feet four inches tall, was a talented basketball player. After basketball practice, Earl would jog home or sometimes catch a ride from residents of Eatonville who knew him well. Sometimes on his way home, Earl would take the backroads that passed by his favorite huckleberry patches. Earl was recruited to play varsity basketball in Tacoma and thought he might become a professional player. He was a gifted clarinet player, too and, at one time, he also aspired to be a jazz clarinetist.

Ultimately though, Earl chose a career in science and attended the University of Washington (UW), earning his bachelor of science in chemistry in 1950. During his undergraduate studies, Earl found polymer chemistry and petroleum-derived compounds quite uninteresting. In contrast, he discovered that doing research on lipids under the guidance of chemistry faculty member Donald J. Hanahan was infinitely more interesting.

On Hanahan's advice, Earl entered the Ph.D. program of the newly established Department of Biochemistry at UW under the mentorship of Hans Neurath, who founded the department in 1950 (and served as its chair until his formal retirement in 1975). Earl learned protein chemistry and identified the peptide bond that is cleaved during the autocatalytic activation of trypsinogen to trypsin, and later

chymotrypsinogen to chymotrypsin. These studies established limited proteolysis as a mechanism for the regulation of enzyme activity ("zymogen activation"), a mechanism that would prove to be broadly used throughout biology, including in the coagulation, complement, and caspase cascades. After receiving his Ph.D. in 1954, Earl then trained as a postdoctoral fellow for two years at Harvard Medical School with Fritz Lipmann, studying tryptophan and later serine activation.

In 1957, Earl accepted an appointment as an assistant professor in the Department of Biochemistry at Western Reserve University (now Case Western Reserve University) in Cleveland, continuing his studies of amino acid activation and intermediary metabolism. In 1962, he returned to UW, joining the faculty of the Department of Biochemistry, where he rose through the ranks and served as chair from 1975 to 1984.

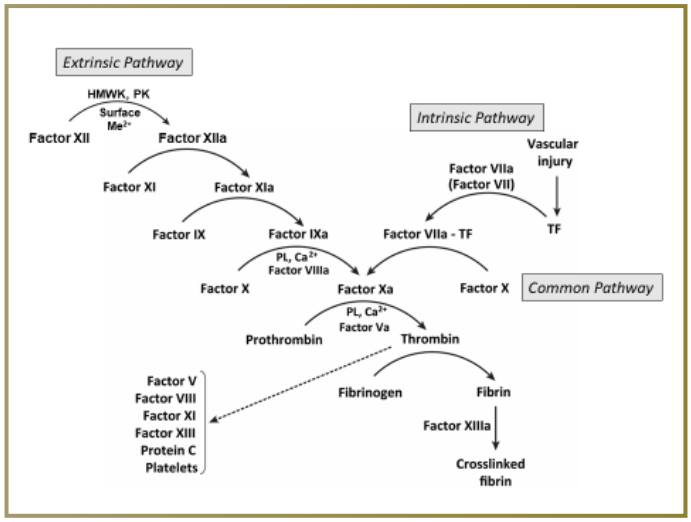

Figure 2 Revised coagulation cascade used in the 1990s, highlighting the intrinsic, extrinsic, and common pathways of the process.

Collaboration with Oscar Ratnoff

In 1953, Oscar D. Ratnoff, a hematologist at Western Reserve University, attended to John Hageman, a freight railroad brakeman. In pre-operative screening prior to a procedure to relieve pyloric obstruction, Ratnoff observed that Hageman's plasma failed to clot in a test tube. The procedure was cancelled because of this abnormal finding. Clotting was restored when a small amount of normal plasma was mixed in with Hageman's plasma. Ratnoff wanted to find out what factor was missing in Hageman's plasma, the absence of which was responsible for his clotting deficiency. Ratnoff wanted to fractionate normal plasma and test which fraction(s), when added back to Hageman's plasma, would restore its clotting in vitro. But one of the media then in use for cation exchange chromatography, carboxymethyl-cellulose, was not readily available commercially at the time. Ratnoff consulted Harlan G. Wood, then the chair of the Department of Biochemistry at Western Reserve, who introduced Ratnoff to Earl because Earl had chemically synthesized carboxymethyl-cellulose previously. Earl recalled that in their initial meeting, Ratnoff was very persistent, and Earl believed that he could not decline.

So, Earl and his technicians Antoinette Iannetta and (Mrs.) Eugene Hussey chromatographed normal plasma over carboxymethyl-cellulose and used a shallow salt gradient to elute the bound proteins, collecting more than eighty fractions in the process. Earl gave all the fractions to Ratnoff, thinking that they would keep Ratnoff busy for a while. Earl was surprised when Ratnoff returned the following day to tell him that one of those fractions contained a protein that restored clotting to Hageman's plasma in vitro. Earl was curious how Ratnoff could identify that particular fraction so quickly. It turned out that Ratnoff first recombined the eluted fractions into pools, and after identifying the active pool, he zeroed in on the individual fractions that made up that pool. Earl was very impressed by Ratnoff's approach, and formality gave way to mutual respect, curiosity prevailed, and plans for subsequent studies were developed. And so began a lifelong collaboration and friendship that lasted more than fifty years. Their initial work led to a hypothesis that described a sequence of zymogen-to-enzyme activation reactions that make up the intrinsic, or contact, pathway of coagulation. The intrinsic pathway was first published in 1962,[1] and then combined with the common pathway, as the *Science* article "Waterfall Sequence for Intrinsic Blood Clotting" in 1964.[2]

This Waterfall hypothesis was controversial at the time, as it contradicted the prevailing theory of Walter H. Seegers and co-investigators, who proposed that several coagulation factors were autocatalytic derivatives of prothrombin, which they dubbed autoprothrombins.[3,4] But based on inconsistencies with the mode of inheritance of the genes for prothrombin, Factor IX and Factor X, it became clear over time that these coagulation factors were not derivatives of prothrombin, but were unique gene products—proteins and enzymes with properties and substrate specificities distinct from those of prothrombin or active thrombin. The Waterfall hypothesis explained the function of these coagulation factors and provided a unifying framework that refocused research in hemostasis with renewed vigor, ushering in a period of tremendous advances in the diagnosis and treatment of bleeding disorders. Except for Factor VIII, which was later shown to function as a cofactor instead of a zymogen, the Waterfall hypothesis was essentially correct as proposed in 1964.

Earl and Ratnoff purified the protein that compensated for the missing factor in John Hageman and named it the Hageman factor (also called Factor XII). They demonstrated that it was the zymogen form of a serine endoprotease that

initiates the intrinsic cascade. John Hageman was glad that the protein was named after him and often appeared in person as a case study in Ratnoff's lectures to medical students. Despite missing Hageman factor, John Hageman did not experience excessive hemorrhaging; but in 1968, twelve days after sustaining fractures of the pelvis and recuperating in the hospital, he died of a pulmonary embolism. Ratnoff and colleagues wrote the closing chapter of this unique case.[5] Hageman factor has since been shown to play important roles in thrombosis[6] and in regulation of the kinin system[7] and is encoded by a human gene designated F12. John Hageman had no known direct descendants, and so the genetic defect had to be studied in descendants of his siblings. To date, only a single G-to-A mutation, located in the splice acceptor site of exon 14 in the F12 gene, has been found in Hageman's family tree. This alteration shifts the splice site by one nucleotide, causing a frameshift in exon 14. In people homozygous for this allele, no immunological cross-reacting material is detectable, suggesting that the defective Hageman factor resulting from this alteration is not secreted.[8]

Bucket Biochemistry

After postulating the Waterfall model, Earl set out to further test the hypothesis by systematic protein chemistry, that is, by purifying each coagulation factor and determining the mechanism of its activation. Because most of the coagulation factors are proteins present in only trace amounts in plasma, Earl's approach was to work out the purification scheme first using bovine plasma, and then confirm with human plasma. For this purpose, two to three times each week, a technician in Earl's lab (one of whom was Donald Hanahan's son Douglas) would drive to a slaughterhouse about twenty-five miles from the UW campus and collect one to two carboys (25–50 liters) of fresh bovine blood. The blood, treated with an anti-coagulant (final concentration 1.34 g/l sodium oxalate, 1700 unit/l heparin, 1 g/l benzamidine-HCl, 10 mg/l soybean trypsin inhibitor), was then processed in the 'Mass Prep' room, a facility located in the basement of J-wing of the UW Health Sciences Building. The bovine blood was first run through a cream separator to remove blood cells. The plasma was further fractionated by barium sulfate precipitation or ammonium sulfate fractionation. A bank of eight to ten Sorvall RC-3B and RC-5 centrifuges would come to life for the following two to three hours. The recovered fractions were then taken to the research lab, where additional chromatography steps with various columns would be carried out. At one time, a massive ten-liter size-exclusion chromatography column, nicknamed the "Space Needle," was set up in the mass prep room for the purification of gram-quantities of von Willebrand factor (VWF), a plasma protein crucial for shear-dependent adhesion of platelets to sites of vascular injury and an endogenous carrier and stabilizer of Factor VIII in the circulation. The purified VWF was sequenced by the group of Koiti Titani, then a member of the department.[9] At that time, VWF was the largest protein ever sequenced by automated Edman degradation.

On many occasions when investigators requested samples of purified coagulation factors from Earl, he would say, "Sure, we have buckets of it." On one occasion, the carboys of bovine blood tipped over in the truck returning from the slaughterhouse and spilled fifty liters of bovine blood onto N.E. Pacific Street, right outside J-wing. Although it was not a biohazard, it was a visually startling incident nevertheless. The Seattle Fire Department was summoned, and the bovine blood was hosed off the street. That year, Earl was awarded the "Ignoble Prize" in the Department of Biochemistry for that embarrassing accident. Nonetheless, using such brute force bucket biochemistry, bovine and human Factors XII, XI, IX, X, VII, plasma prekallikrein, protein C, protein S, and bovine Factor VIII were all purified and characterized in Earl's lab. These studies left no doubt that the coagulation factors described in the Waterfall hypothesis are, in fact, distinct proteins and not derivatives of prothrombin.[10] The autoprothrombins were trace contaminants of homologous vitamin K-dependent coagulation factors in Seeger's prothrombin preparations, misinterpreted as derivatives of prothrombin.

Delving into Molecular Biology

In 1975, based on their studies of the biogenesis of immunoglobin light chains,[11] Blobel and Dobberstein conjectured that the sequence at the N-terminus of the precursor to any protein destined for secretion directs its transport across the membrane of the endoplasmic reticulum (ER)—and, thus was born the signal sequence hypothesis. Because most of the coagulation factors are synthesized and secreted by the liver, Earl wondered whether the coagulation factors bore signal sequences and, if they did, what those sequences were. Because signal peptides are removed during transport across the ER membrane, they remained only on the precursor forms synthesized in the absence of microsomal membranes in vitro. Accordingly, Ross MacGillivray in the lab immunoprecipitated bovine liver polysomes with anti-bovine prothrombin antibodies and extracted the mRNA from the enriched polysomes. He then translated the mRNA in the presence of radioactive amino acids in a rabbit reticulocyte cell-free protein synthesis system lacking microsomes. In vitro synthesized prothrombin was immunoprecipitated with antibodies and sequenced by automated Edman degradation. Sequentially released radioactive amino acids identified an N-terminal precursor sequence on bovine prothrombin that was more than twenty-nine residues in length,[12] longer than most signal peptides known at the time. Because the

enriched polysomes contained full-length mRNA for bovine prothrombin, the enriched mRNA was reverse transcribed into cDNA and cloned in a plasmid vector in collaboration with Savio L.-C. Woo, who had earlier completed his graduate training with Earl. Subsequent sequencing of the cDNA encoding human prothrombin confirmed that the nascent polypeptide is actually *prepro*-prothrombin, that is it contains an N-terminal precursor sequence of forty-three amino acids that includes a signal peptide (*pre*-sequence) of twenty-six amino acids, followed by a *pro*-sequence of seventeen amino acids,[13] which was later shown to be a motif conserved among vitamin-K-dependent coagulation proteins that directs the nascent polypeptides for γ-carboxylation, a post-translational modification crucial for binding calcium. The *pre*-sequence is removed by signal peptidase in the ER and the *pro*-sequence is removed by a furin-like endoprotease in the late Golgi cisternae prior to mature prothrombin secretion.

These initial studies were conducted prior to the availability of genome-wide cDNA libraries, and therefore, polysome immunoprecipitation represented a successful alternative approach for enriching for the mRNA from which to generate the cDNA for trace proteins. In this way, Earl's research group entered the realm of molecular biology, despite the opinion of the Study Section that reviewed Earl's grant renewal application and recommended that Earl should stick to what he knew how to do (protein chemistry) and not delve into what he had no experience in (molecular biology). In spite of these discouraging comments, Earl and his group eventually cloned cDNAs for more than thirty-eight proteins. Among these was the cDNA for Factor IX, which was cloned by Kotoku Kurachi and patented for the production of recombinant Factor IX in the treatment of hemophilia B.[14] A team under the direction of Kurachi and Earl established the complete sequence of the human Factor IX gene, manually sequencing both strands of the Factor IX gene, which had since served as the reference sequence for the identification of more than one thousand mutations and variants identified in hemophilia B patients.[15] To have not seized the opportunity to explore molecular biology or other aspects of the unknown would have been against Earl's preferred fearless approach in science.

Earl's Last Experiment at the Bench

In 1980, when cDNAs for bovine prothrombin and fibrinogen were cloned by Ross MacGillivray and one of us (Dominic Chung) in Earl's lab, Earl was tremendously excited about the progress. He came into the lab every day to find out the latest details of DNA sequencing. On one occasion, Ross suggested that he might consider performing Maxam-Gilbert DNA sequencing himself, to which Earl said, "Why not?" and, turning around, asked, "Dominic, what time do we start tomorrow?" After ascertaining that Earl really meant what he said, Ross and Dominic located safety goggles for him, but disposable laboratory-grade gloves large enough for Earl's big hands were not immediately available. Ultimately, commercial kitchen gloves for dishwashing were used instead. Earl cleared three days from his schedule and carried out base-specific cleavage reactions according to the Maxam-Gilbert method on a radioactive fragment of the cDNA for the γ chain of human fibrinogen and ran a sequencing gel. As he read out the sequence, Dominic recorded it on paper. After he finished reading the film, he asked Dominic to re-read the same film to check against his reading. In the end, Earl said with a smile, "You have not made any mistake!"

Background Actor

Also in 1980, Gordon A. Vehar, a postdoctoral fellow in Earl's lab, purified bovine Factor VIII. Thereafter, he joined Genentech Inc. (and, much later, Biomarin Pharmaceuticals, Inc.) and was instrumental in developing recombinant tissue plasminogen activator (tPA) and then human Factor VIII for therapeutic use. The tPA, a fibrinolytic reagent, was most effective when administered soon after the onset of a heart attack, an ischemic stroke, or a pulmonary embolism. Seattle boasted the fastest response time of its emergency response team in any U.S. city, and there was tremendous interest in this "wonder drug" and "clot buster" there. The then-science and health reporter Brook Stanford from local TV station KOMO interviewed Robert A. Bruce, the head of cardiology at UW at that time, and he brought Brook to speak with Earl. After a few minutes, they emerged from Earl's office and went into the lab and asked visiting scientist Akitada Ichinose to bring out the sample of recombinant tPA Earl had received from Genentech, which was intended for use in a collaborative study. Brook wanted the camera focused on the tPA sample while he narrated the commentary. Right before filming, Brook wanted to have someone in the background so that the lab would not look deserted. Earl put on a lab coat and went into the background, and with his back to the camera, started to look busy at the lab bench. After filming, the KOMO team then rushed back to the studio to prepare the segment for broadcast on the 5 pm news that same day. In the aired segment, Earl was in the background pretending to transfer something from an Erlenmeyer flask with a Pipetman P1000. But the flask was empty and the P1000 did not have a transfer tip—this subtle tease was typical of the kind Earl often pulled.

Earl's Role in Recombinant Factor VIIa

Back in the mid-1970s, Walter Kisiel, then research faculty in Earl's group, purified and studied the functions of the

zymogen Factor VII and its activated form, Factor VIIa.[16] After Walt established a procedure for purifying human Factor VIIa, Earl asked him to send three milligrams of Factor VII (two milligrams of zymogen Factor VII and one milligram of Factor VIIa) to Henry S. Kingdon at the University of North Carolina at Chapel Hill, and he infused the Factor VII into a beagle with hemophilia after it had undergone gingival biopsy. Henry had been one of Earl's earliest trainees. The Factor VII restored hemostasis and prevented bleeding in this canine model. Based on this finding, Earl suggested that Walt should extend these studies to hemophilia A (Factor VIII–deficient) patients with inhibitors. After obtaining regulatory approval on a compassionate-use basis, Ulla K. E. Hedner of Malmö, Sweden, collaborated with Walt to purify pyrogen-free human Factor VIIa, which was infused into two hemophilic patients with high-titer inhibitory antibodies to Factor VIII. The purified Factor VIIa stopped muscle bleeding in one patient and prevented bleeding after tooth extraction in the second.[17] These studies formed the basis for the use of Factor VIIa as a bypass reagent to restore hemostasis in hemophilia patients with inhibitors. The cDNA for Factor VII was cloned by Frederick S. Hagen and coworkers at ZymoGenetics Inc., which initiated production of recombinant Factor VIIa; it was later mass-produced by Novo Nordisk A/S and marketed as NovoSeven for therapeutic use.[18] From 2011 to 2023, the revenue from the sale of NovoSeven was about $1 billion U.S. dollars per year.

ZymoGenetics

In 1981, Earl, Benjamin D. Hall from the Department of Genetics at UW and Nobel laureate Michael Smith from the University of British Columbia in Canada, founded ZymoGenetics Inc, one of the early biotechnology companies in Seattle. One of its projects was to develop an expression system for the Danish pharmaceutical company Novo Nordisk to manufacture recombinant human insulin in yeast. Hedging their bets, Novo Nordisk also contracted with another early biotechnology pioneer, Chiron Corporation in Emeryville, California, to do the same.

Successful development of such systems by both companies enabled Novo Nordisk to transition from extracting insulin from porcine pancreases to producing authentic human insulin from yeast. In 1988, Novo Nordisk acquired ZymoGenetics and, in honor of Earl's contributions, endowed the Earl Davie and ZymoGenetics Chair in Biochemistry at UW. ZymoGenetics continued as a center for research and later developed additional recombinant proteins, including human Factor VIIa and human thrombin for therapeutic use. In 2000, ZymoGenetics was spun off from Novo Nordisk as a public company and, in 2001, the company dedicated a new facility, the Earl Davie Building, on Eastlake Ave E., next to its Seattle headquarters. In 2010, ZymoGenetics was acquired by Bristol-Myers Squibb and then ceased operations in 2019.

Research and Teaching

One of Earl's important contributions to science was his mentoring of generations of scientists, who themselves have made countless important contributions to our understanding of the biochemical basis of thrombosis and hemostasis. For Earl, research always went hand in hand with teaching and mentoring, but research was always preeminent. In this way, teaching was accompanied by insight and perspective. He trained more than eighty pre- and postdoctoral fellows, including post-Ph.D. and post-M.D. senior fellows, all of whom make up his extended family in science. Many of his trainees continued to collaborate with Earl on various projects after they left his lab. Many stayed in contact, and Earl was interested in how they fared in science and otherwise, much like with blood relatives (no pun intended!).

Every member of Earl's lab had his or her own project, and there was no internal competition. At its peak, Earl's research group had sixteen members. He recognized that there was an element of serendipity in science, but one could not get lucky without effort, and Earl encouraged all trainees to try hard and with their eyes wide open. Everyone, including Earl, worked long hours and often on holidays. Protein purification and column chromatography needed careful tending, even at odd hours. Those who worked late were often rewarded with a stunning view of Mount Rainier from Earl's lab in J wing bathed in a warm golden glow in the sunset. Regrettably, construction of K wing of the medical school complex took that view away. Research in Earl's lab also nurtured and inspired undergraduate students. Knowing the tremendous influence his own undergraduate research had on him, Earl invited outstanding undergraduate students in the biochemistry lab course to participate in research in his lab. In 1979, Sandra J. F. Degen, then a pre-doctoral trainee in Earl's lab who served as teaching assistant in the lab course, introduced the first hands-on experiment on recombinant DNA to the undergraduates. In subsequent years, other techniques in molecular biology, including radioactive DNA sequencing and the polymerase chain reaction, were also added to the course's curriculum, complementing concepts discussed in the lecture courses with practical experience.

Nationally, Earl and Ratnoff initiated the Gordon Research Conferences on Hemostasis, a series of meetings that has been ongoing since 1973. Locally, in honor of his mentor Hans Neurath and with support from ZymoGenetics, Earl established UW's annual Hans Neurath Lectureship, which brings prominent scientists to campus to promote excellence in science. In honor of his parents, Earl and his wife, Anita,

also established an Honor Cup Scholarship for academic excellence at Eatonville High School. Earl attended the annual graduation and award ceremonies and met the scholarship recipients. Most of them continued their education, and their ranks include engineers, mathematicians, physicians, principal dancers, and sculptors, to name a few. During one of his visits to Eatonville High School, Earl showed photographs of wildlife he took on a trip to Africa to promote conservation. On another occasion, Earl brought with him to Eatonville High School his close friend, UW biochemistry professor and Nobel laureate Edmund (Eddy) Fischer to advocate for science.

In 2006, the Centre for Blood Research at the University of British Columbia, under its then director (and Earl's former trainee) Ross MacGillivray, established the annual Earl W. Davie Symposium, which gathers prominent scientists for a one-day symposium to discuss and exchange ideas on Earl's favorite topics, hemostasis and thrombosis. Earl attended almost every symposium and enjoyed those meetings tremendously; he last attended the symposium in November 2019, about seven months before he passed away.

At work, Earl was gracious and rigorous—the very antithesis of the self-satisfied braggart. He was passionate about research but bored by bureaucratic details. Perpetually reluctant to voice any kind of dissatisfaction, Earl quietly sidestepped some of his administrative duties by escaping to the laboratory, to quiz his M.D. trainee on gout, or to talk about fish farming, or to discuss the robin that nearly fell off the branch after eating too many fermented berries on the mountain ash outside his window, or the time he threw a snowball at Eddy Fischer while skiing at Snoqualmie, or the time he was pooped on by a bald eagle right at his front door as he was departing for work, or the first time he had sushi with *uni* (sea urchin) in Japan, or the occasion he and his daughter Karen had a papal audience with Pope John Paul II, or just to have a cup of tea and talk about "clean living" with long-time associate Kazuo Fujikawa. Quick to laugh and to tease, he was fond of shooting the breeze with almost anyone willing to lend an ear.

Earl and his laboratory attracted researchers from around the globe, particularly Japan. Through such visitors, Earl developed a taste for sushi, which he often served at lab parties. He kept in contact with his far-flung colleagues and acquaintances through frequent travel; in later years, he was accompanied by his daughter Karen and often by his close friend Eddy Fischer.

Growing up, Earl was very close to his older brother, John, who served in the U.S. Navy during World War II. He was one of ninety-two servicemen who died on the USS *Belleau Wood* when it was attacked by a kamikaze pilot in the Battle of Leyte Gulf in the Pacific Theater in October 1944 and was memorialized on the Walls of the Missing at the Manila American Cemetery and Memorial. In the mid-2000s, Earl befriended the Filipino custodian who cleaned his office every day. Earl learned in a casual conversation that his friend would be returning to the Philippines for a vacation. Earl mentioned his brother and the memorial. To Earl's surprise, his friend visited and took photos of the Manila American Cemetery and the Walls of the Missing and gave those photos to Earl on his return to Seattle. Earl treasured those photos.

Interests and Hobbies

Earl was an avid fisherman and spent his vacations with family and friends fishing at Langara Island in British Columbia, his favorite spot for salmon fishing. Dressed in a survival suit and sometimes braving six-foot waves, Earl would use GPS to pilot the boat and stay on the water the entire day. He enjoyed the pristine scenery of the Queen Charlotte Islands, the orcas breaching in the distance, the occasional bubble feeding of the humpback whales, the bald eagles, and the excitement of what he would catch that day.

Although at one time Earl aspired to be a jazz musician, he liked many different genres of music, including classical music. He often listened to jazz while driving to work and classical music while reading in his office. He had a large collection of music on vinyl LPs, and as his turntable fell into disrepair, he had several of his favorite recordings transcribed from LPs to CDs so that he could continue to listen to his favorite performers for these compositions. Among these were

Figure 3 Earl displays his catch from fishing waters off the Queen Charlotte Islands in British Columbia, Canada.

recordings of Donizetti's operas *L'elisir D'amore* and *Lucia di Lammermoor* (the latter by Lily Pons).

Earl retired and became an emeritus professor in 2012 but remained active in research. He passed away at age ninety-two in Bellevue, Washington, on June 6, 2020. In the eulogy at Earl's memorial, the pastor compared Earl to an explorer, curious about the unknown and excited by uncertainty, exemplified by his interest in science and the excitement of what he would discover. Truer words were never spoken.

Earl was buried in the Alder cemetery next to his parents, Charles and Teckla, and beside his daughter Karen, who preceded him in death about six months earlier. A memorial symposium sponsored by the Department of Biochemistry to celebrate his accomplishments and legacy took place online in April 2021 (during the then ongoing SARS-CoV-2 pandemic). Together with his surviving family members, his extended family in science are greatly saddened by his passing.

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