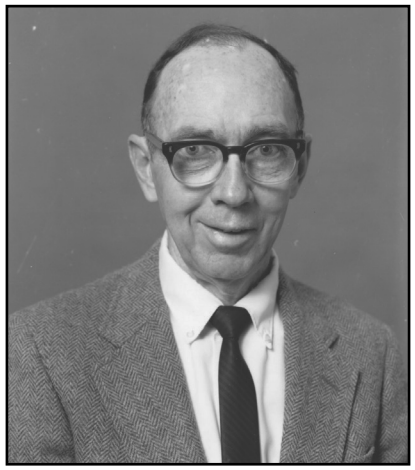
RUSSELL DOOLITTLE



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Russell Doolittle, an illustrious colleague and treasured faculty member who made extraordinary contributions to the field of molecular evolution and the study of the clotting of blood, died on October 11, 2019, from complications of metastatic melanoma. He was 88 years old.

Doolittle was born on January 10, 1931 in New Haven, Connecticut. He attended Wesleyan University in Connecticut from 1948 to 1952. He then was drafted into the U.S. Army and arrived in Korea a few days before the armistice in July 1953. After his discharge from the Army, he married Frances Tynan in 1955, who became his beloved wife for 64 years. In 1957, Doolittle received a master's degree in education from Trinity College in Hartford while teaching science at New Milford High School. He then entered a doctoral program at Harvard Medical School's Department of Biological Chemistry, where he conducted research in J. Lawrence Oncley's laboratory. Following his graduation in 1961, Doolittle spent a year teaching at Amherst College before the siren song of scientific research drew him to the Blombäck laboratory on a postdoctoral fellowship from the National Institutes of Health. In 1964, he joined S. Jonathan Singer's laboratory as an assistant research biologist in the Department of Biology at the University of California San Diego. In 1965, he accepted the position of assistant professor in what is now the Department of Chemistry and Biochemistry.

At UC San Diego, Doolittle resumed his study of the amino acid sequences of fibrinopeptides, the short fragments of protein released from the molecule fibrinogen that circulate in the blood. He began this work during his two years as a postdoctoral fellow in Birger Blombäck's laboratory at the Karolinska Institutet in Sweden. At that time, he and Professor Blombäck showed that the differences in the amino acid sequences of these short peptides between animal species, which could be readily determined with the methods available at the time, provided indications of evolutionary relationships. When Doolittle took up these studies at UC San Diego, he set up a collaboration with the San Diego Zoo to obtain blood drawn from animals, which parenthetically led to an article in a local periodical about "Dr. Doolittle" at the zoo.

During his time in Sweden, Doolittle realized that the rate at which the sequence of amino acids in fibrinopeptides changed over time provided information about the history of speciation over tens of millions of years—the period of time over which the separation of species within the different orders of animals occurred. Choosing the cetartiodactyla order of pigs, camels, llamas, mule deer, reindeer, red

deer, cape buffalo, bison, goats, and sheep, and comparing the sequences of the fibrinopeptides from them, Doolittle created a family tree for these species. He then used sequences of fibrinopeptides to establish a phylogeny of the primate order of macaque, green monkey, baboon, drill, gibbon, chimpanzee, and man. Both of these efforts were seminal studies in the nascent field of molecular evolution, which has exploded over the last 50 years.

Doolittle continued his study of molecular evolution even after he turned his attention to fibrinogen, rather than its fibrinopeptides. He was among the first to create an online compendium of all the amino acid sequences available at the time so that he could update the data routinely rather than rely on the publication of printed versions. This personal project was the forerunner of the massive online data banks available that now employ large staffs and are generously supported by the governments of the United States and the European Union. He also studied the amino acid sequence of the complete molecule of fibrinogen from the lamprey, the member of the phylum of chordates most distant from mammals. This study's results allowed him to extend his quest for the ancestors of fibrinogen into invertebrates. Eventually, using the techniques of molecular genetics, which were just then being developed, Doolittle was able to find a protein in sea cucumbers that shares a common ancestor with chordate fibrinogen, thus extending its evolutionary history.

With his interest in the evolution of proteins, Doolittle continued aligning sequences of amino acids and building family trees. Eventually, he created a phylogeny that included the divergence between plants, fungi, and animals dating from a billion years ago. He also advised others who were doing similar work around the world. This lifelong interest in evolution prompted him to engage in public debate with advocates of "creation science." He retained his files holding his arguments throughout his lifetime.

In the 1970s, the main emphasis of his research shifted from molecular evolution to fibrinogen, the molecule in the blood that produces the clots that staunch bleeding but, when accumulated in the wrong places, can cause strokes and heart attacks. He set out to determine the sequences of the amino acids in the three polypeptides that comprise human fibrinogen, a total of 1,810 amino acids in all. At the time, this was a monumental undertaking that tested the limits of the existing techniques, but Doolittle accomplished it.

Eager to do more, Doolittle set out to discover clues to the three-dimensional structure of fibrinogen within the sequences, which many

considered a waste of time. Still, with careful examination, he deduced that a molecule of fibrinogen consisted of three balls of protein connected by two long cables of protein, and that a large portion of one of the polypeptides was a structureless coil extending out into the solution. On the basis of this proposed structure, Doolittle proposed a detailed molecular mechanism as to how the fibrinogen, once the fibrinopeptides were removed, could polymerize into the long fibers that cause the blood to clot. His proposal for the structure of fibrinogen and the way in which it polymerized were soon validated by the electron micrographs of Robley Williams. These micrographs, however, did not validate his predictions of the molecular details of the process, so Doolittle designed a series of elegant experiments, the results of which were consistent with his proposal for those details. He realized, however, that the ultimate validation of his mechanism would require an atomic structure of fibrinogen, which up to that time had defied the techniques of crystallography, which require crystallizing the molecule, exposing a crystal to a beam of X-rays, and submitting the pattern of diffraction to analysis. These are complex procedures that he had not yet performed. Undaunted, Doolittle learned the methods and persevered until he obtained several atomic structures, including that of the entire molecule of fibrinogen, and validated his proposals. In this way, he provided a final proof of his molecular explanation for the clotting of blood.

One of Doolittle's most important and broadly relevant contributions was his work on comparative protein sequence and structure. In the days before DNA sequencing and gene cloning became universal tools of biology, Doolittle established the first searchable computer database of protein sequences by using snippets of data he received from around the world. With the introduction of cloning and DNA sequencing, molecular biologists were also getting snippets of gene sequences; however, they had no idea what proteins might be encoded by these newly cloned pieces of DNA. Doolittle understood that he could link the two. In doing so, he allowed molecular biologists to understand the function of the genes they were cloning. Doolittle also provided key new insights into the evolutionary conservation of genes and the nature of gene families. He established the first building blocks of the human genome project and put our understanding of biology at a gene level into hyperdrive in the 1970s and 1980s, setting the stage for future discoveries.

For the elegance and importance of his work, Doolittle was elected a member of the National Academy of Sciences in 1984. He received a

Guggenheim Fellowship in 1984, the Paul Ehrlich Prize in 1989, and the John J. Carty Award for the Advancement of Science in 2006. Over the years, he was chosen to present 18 named lectures to various university faculties and scientific societies.

An amazing aspect of Doolittle's scientific career was his insistence on being at the bench performing or directing the experiments himself. He sat with his staff for an hour or more at a time, double-checking the transcription between the original publication and his growing atlas of amino acid sequences. He either performed or directly supervised his assistants in the thousands of digestions, chromatographic separations, chemical reactions, and analyses required to determine the amino acid sequences of the polypeptides of fibrinogen. He went with his students to New England to gather samples from the lampreys for his studies. He mastered the novel, complicated procedures of molecular genetics necessary to discover the ancestor of fibrinogen. He, as well as his students, performed the synthesis of the peptides to provide evidence for his proposals that explained the polymerization of fibrinogen. When Doolittle realized that crystallography and obtaining the patterns from the diffraction of X-rays and their analysis were needed to validate his proposals, techniques to which entire laboratories are exclusively devoted, he mastered them with the help of scientists at Joe Kraut's and Xuong Nguyen-Huu's laboratories at UC San Diego. Alongside his graduate student and postdoctoral fellow, he made crystals, collected diffractions at the synchrotron at Berkeley, applied the Fourier transforms, and, on the computer screen, inserted the molecular models into the electron densities that resulted.

In addition to his time spent in the laboratory and lecturing, Doolittle served UC San Diego at large. Soon after becoming a member of the Department of Chemistry and Biochemistry, he played a major role in establishing the basic science programs for the undergraduate curriculum, as well as the basic science curriculum in the School of Medicine. He was chairman of the Department of Chemistry from 1981 to 1984. During his tenure, Bill Trogler, Don Tilley, Joe O'Connor, and Dan Donoghue accepted offers and joined the faculty. In addition to serving on 25 committees of the Academic Senate over the last 51 years, he was also chairman of the Academic Senate, chair of the Executive and Policy Committee, and member of the university-wide Academic Council in the academic year of 1977/1978. During his tenure, a move among the members of the Academic Senate to censure Chancellor William McElroy was rapidly gaining adherents. Doolittle approached his role as chairman of the Academic Senate with

evenhandedness and refrained from voicing his own opinion on the subject. He allowed the various committees to investigate the complaints and accusations and, following the distribution of their reports, oversaw the vote on the censure, which was in favor and which eventually led to the Chancellor's resignation. At the end of Doolittle's term as chairman, after all of the exhausting and time-consuming soul searching, one of his colleagues pinned a sign on his door that read "Remember Cincinnatus," which Doolittle left in place for several months as a reminder that he wanted to return to his research.

Among one of the many unusual aspects of Doolittle's life was his decision to run for the House of Representatives in 1968. When the Democratic Party of his district failed to find a candidate in what was then a deeply Republican area, Doolittle volunteered. He received 45 percent of the vote in the Democratic primary, but lost to a much more conservative Democrat in a district that extended into Orange County at the time. The most peculiar plank in his platform was related to firearms. While Doolittle conceded that the Constitution seemed to guarantee a right to bear arms, it said nothing about ammunition. Consequently, he proposed that there should be a number of strict regulations on its sale. The voters failed to send him to Washington.

Doolittle was devoted to his wife Fran and their sons Larry and Will. He often engaged his sons in mutual endeavors—recruiting them as assistants in his many do-it-yourself projects around the house or involving them in special collaborations. Consequently, Larry Doolittle became interested in computing and wrote programs in his father's laboratory, aligning sequences and computing evolutionary distances. He also helped his father construct an automated amino acid sequencer. Will Doolittle once rebuilt the engine of the family Volkswagen Beetle with his dad.

Russell Doolittle also enjoyed running during his younger years. After enrolling in a health study at the university, he began participating in marathons. He made California's top 100 marathon runners list in his age group, and his fastest time was 3 hours and 20 minutes.

Doolittle was known to have high standards for scientific research, a willingness to do the work to meet those standards, and expectations of the same from his peers. When relaxing, he was an entertaining raconteur with many amusing stories, which he presented in a way guaranteed to elicit happy laughter from his audience. He was also a mentor to younger scientists who were drawn to him and found him willing to listen and give advice freely. He always had a good word to say about his younger colleagues, and he was an enduring friend.

Doolittle is survived by his wife Fran, his sons Larry and Will, and four grandchildren.

Elected 1992

Jack Kyte, Robert Fahey, and Joseph Watson
Emeritus Professors, Department of Chemistry and Biochemistry
University of California San Diego

Note

The memoir and components of this memoir were used in the UCSD campus announcement to all faculty and staff as well as printed in the memorial program.