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Editorial

A tribute to Robert Steven Ledley

As *Computers in Biology and Medicine* begins is fortieth year of publication,[1] its Founding Editor, Robert Ledley, steps down as Editor-in-Chief. Pausing to consider this remarkable man and his accomplished career illuminates the histories of both the discipline of biomedical computing and of this journal, and may well provide insights into the forces that will shape both in future. The following comments are heavily indebted to the work of Joseph November, whose Ph.D. thesis for Princeton's Program in History of Science is serving as the basis of a new book about the early history of computers in biomedicine [1]. November's work is a compelling (and fun) read for anyone working in this field, and documents the fragility of a new discipline and the careers of the people creating it—and the magic mix of talent, determination, and sheer good luck that marks the difference between success and failure (or, a delayed and muted success). It also illumines the critically important role of larger social forces, particularly that of government as a patron of science and technology.

A short description of a career, focusing only on achievements, can not do justice to the full complexity and difficulties of its protagonist's working life; no professional history of note is a smooth arc, moving from success to success. Equally, it is difficult to give due justice to the effect of specific individuals, institutions, and historical events. Nevertheless, I attempt here to at least suggest the complexity of events surrounding Robert Ledley's achievements, give due credit to some of the people who influenced him in important ways, and portray the exciting opportunities he has had to interact with some of the best minds of his time. For the full tapestry, I refer you to November's book.

Robert Steven Ledley was born in 1926 in Flushing Meadows, NY. A graduate of the Horace Mann School, he entered Columbia University in 1943, majoring in physics (but with strong interests in mathematics and engineering). Diverted by parents who were dubious about making a comfortable life from a career in physics, he followed a path traditional to his family, and enrolled in NYU's College of Dentistry. Continuing to attend evening courses in physics and mathematics at Columbia, he was described by one of his professors, Isidor I. Rabi [1898–1988] (1944 Nobelist in Physics for the discovery of NMR) as "the only physics student he knew who could pull a tooth." The physics faculty at the time included a dazzling roster of at least eight Nobel laureates, many of whom taught Ledley (including Hans Bethe [1906–2005], Enrico Fermi [1901–1954], and John Wheeler [1911–2008]). Few knew at the time that their presence was part of the early staging operations for the Manhattan Project.

In 1950, the Korean War intervened, shortly after Ledley completed his studies at Columbia. Armed with a DDS and a Masters Degree in theoretical physics (having exhausted Columbia's offerings in mathematics and physics), Robert elected to join the Army Medical Corps as an alternative to likely conscription into the infantry. Serendipity: the Corps was looking to improve dental prosthetics, and Ledley's unusual background was ideal. He ended up at Walter Reed Army Hospital in Washington, DC, where his success in devising mathematical models for dental pressure led to other assignments, including work on an artificial heart valve. Shrewdly realizing "never to volunteer," he was able to spend much of his time reading physics and mathematics.

In 1952, he transferred to the National Bureau of Standards (NBS, now known as the National Institute of Standards and Technology, or NIST) to learn how to program a first-generation electronic computer, the SEAC (Standards Electronic/Eastern Automatic Computer), in order to develop a remote-controlled aircraft guidance system. Such early machines forced their users to understand their internal structure and operation, as well as the numerical algorithms employed. Robert began to simulate his dental pressure models in his free time. It was at this moment that he discovered his mission in life—to explore the "application of computers to biomedical problems."

Ledley's army service came to an end in 1952, but he stayed on at NBS, where he studied logic circuit design and Operations Research (OR), with military applications in mind. Losing his post (along with many others) due to a 1954 budget cut-back at NBS, Ledley moved to the Strategic Division of the Operations Research Office at Johns Hopkins University, where he continued to pursue his interest in OR, applying it to war gaming. During this period, he met physicist George Gamow [1904–1968] (originator of the "Big Bang" cosmological theory), who had turned his prodigious talents to the problem of figuring out how DNA/RNA coded protein structure. Recognizing Ledley's abilities and the potential of OR and computerized logic, he inducted Robert into his exclusive "RNA Tie Club," each member of which was given the name of an amino acid (and a necktie with that name upon it): Ledley was "ASN" (Asparagine). This placed him in the heady company of GLY (Richard Feynman [1918–1988]), LEU (Edward Teller [1908–2003]), PRO (James Watson [1928–]), TRY (Max Delbrück [1906–1981]), TYR (Francis Crick [1916–2004]), and VAL (Sydney Brenner [1927–]), among others. Ledley's subsequent application of Boolean logic and OR methods outlined the combinatorial enormity of Gamow's decryption task, but did not lead to a solution of the amino acid coding scheme; Gamow drifted away from Ledley, turning to statistical approaches (which also failed him; this problem was to be solved by Marshall

[1] The Internet has just celebrated its 40th anniversary as well.

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Nirenberg [1927–] and others, starting in 1959, using clever radioisotopic experiments).

Still involved with military OR work at Hopkins, Ledley kept alive his interests in computerizing medicine, presenting two relevant papers at the Operations Research Society's Fourth Annual Meeting in Washington, DC, in 1956. Another attendee, William J. Hovarth, of Airborne Instruments Laboratory (AIL), Inc., also presented a paper on a medical topic; it was several weeks later that a younger colleague of Hovarth, a radiologist named Lee Lusted [1922–1994], called Ledley "out of the blue." This was to lead to a collaboration of central importance in both men's careers.

Lee Lusted, a remarkable and protean figure in his own right, would later found the Society for Medical Decision Making (and its excellent journal, *Medical Decision Making*), and act as kindly mentor to many young physicians and scientists. An interdisciplinarian like Ledley (with experience in both radar development and electronics, as well as radiology), his career had also been shaped by wars (WW II, Korea) and the draft. At the time of contacting Ledley, faced with conscription into the Army Medical Corps, he had moved from an academic post in radiology at the University of California, San Francisco, to assume an active duty post in the US Public Health Service. He was posted to the Radiation Department at the NIH Clinical Center in Bethesda, Maryland. As had been the case with Ledley at NBS, he had sufficient free time to pursue other interests, which had led to his consulting for firms such as AIL, which was developing a device to assist in screening for cervical cancer. Lusted and Ledley met at NIH, and recognized their shared interests, but then Lusted moved on to a new post at Rochester, and the two continued to work independently for a time.

One important early source of support for computer research was the US Air Force's Air Research and Development Command (ARDC). Eager to soften the perception of computer technology as being primarily associated with warfare, ARDC requested that the National Academy of Sciences-National Resource Council's (NAS-NRC) Division of Medical Science convene a symposium on the application of computers to biology and medicine. A preliminary meeting led to another one-day planning meeting (the "Roundtable Conference on a Symposium on the Use of Computers in Biology and Medicine") in early 1957. Although this Roundtable failed at its primary task (to plan for a larger meeting on biomedical computing), November describes it as a "watershed," the first meeting of parties of influence from which major later efforts would flow. It also marked a pass-off of sorts, analogous to ARPA transforming the ARPAnet into a privatized civilian entity, the internet, in that ARDC passed the baton for promoting civilian biomedical computing to NAS-NRC. This did not last long, for by the early 60 s the baton had been passed again, this time to the NIH, where Director James Shannon was an enthusiastic (and ultimately powerfully effective) agent of change in support of biomedical computing. Biology was not yet prepared for the requisite shift in mindset, though. Shannon had already offered 10 different universities to fund the acquisition and maintenance of a computer facility for their biology departments, if courses in mathematics and computing were made mandatory, and all 10 had declined the offer (imagine that happening today!).

Lee Lusted was among the 1957 Roundtable's 20 participants, as was the Olympian Howard Aiken [1900–1973] of the Harvard Computation Laboratory (inventor, with the help of Grace Hopper [1906–1992] and others, of the Mark I, II, III, and IV computers).

Lusted was an enthusiastic proponent of applying computers to medical diagnosis, and Aiken clearly shared Lusted and Ledley's views on the need to "mathematize" biology. Among the train of events following the Roundtable were: the appointment of Robert Ledley (working part-time for NAS-NRC) to conduct a survey on the existing and planned uses of computers in biomedical research, and to create a text to introduce workers to the field; and, the appointment of Lee Lusted as Chair of a committee advising Ledley on these two tasks. Ledley moved to a faculty appointment at George Washington University at this time, and was also acting as a consultant in mathematics for NBS. He found a powerful patron in the form of Senator Hubert Humphrey, who supported the survey task with resources and letters of introduction. Ledley's survey would later have a major impact upon the content of a report to the US Senate, issued in 1960.

It was shortly after the Roundtable that Lee and Robert began to collaborate in earnest. Ledley suggested the applicability of a favored tool from OR, Bayes' Theorem, to the medical diagnosis problem. This led ultimately to their 1959 paper in *Science*, "The Reasoning Foundations of Medical Diagnosis [2]." A recent search in the *Science Citation Index* [3] revealed that this article had been cited 389 times, a rather modest number for some disciplines—and a powerful demonstration of the limitations of taking an overly simplified approach to bibliometric analysis, as this publication is widely (and properly) regarded as a foundational work in the field of computer-based medical diagnosis (it was given its due in a 1991 issue of *Medical Decision Making*, containing a Festschrift in honor of Lee Lusted, which included a citation analysis [4]). The article prompted a flood of reprint requests, and was translated into Russian two years later.

Less often cited (but important in its way) was Ledley's second *Science* article of 1959, "Digital Electronic Computers in Biomedical Science, [5]" which conveyed the initial conclusions he had drawn from the NAS-NRC-supported survey. Appearing in the November 6 issue of *Science*, Ledley's article was followed immediately by another, entitled "Further Evidence of Vegetation on Mars." Joshua Lederberg [1925–2008], a young Nobelist working at Stanford at the time, was interested in exobiology, read the Mars article, and noticed (and read) the Ledley piece.[2] He immediately enrolled in his first computer programming course, starting down a path that led to substantial contributions to artificial intelligence, through the DENDRAL project [6]. More broadly, the article served as a guide to NIH's Advisory Committee on Computers in Research (initially chaired by Lee Lusted) as it led that agency's multimillion-dollar effort to computerize biology and medicine in the early 1960s.

The second of Ledley's tasks for NAS-NRC, a textbook, finally appeared in 1965, as *Use of Computers in Biology and Medicine* [7]. It had not been an easy project for Ledley; NAS-NRC reviewers of the mathematical sections of the initial 1960 draft had been harsh, but Ledley had persisted. One of the first texts in its field, the ambitious 965-page tome led off with prefaces from the NAS-NRC and Lusted, and comprised four sections: the first two were an introduction and an overview of the design and function of digital and analog computers of the day (pre-integrated-circuit!); the third examined, in considerable detail, a wide variety of specific biomedical applications; the fourth and final presented a broad survey of applied mathematics and statistics.

In 1960, Ledley began to part company with NAS-NRC, founding, with their assistance, the non-profit National Biomedical Research Foundation (NBRF), which was to remain his permanent professional home. In 1970, he shifted himself (and NBRF) to Georgetown University.

Challenges aside, Robert Ledley has had a long and productive career. He was founding Editor-in-Chief of four peer-reviewed research journals (including this one), obtained over 60 patents, contributed to over 350 articles and abstracts, and wrote or edited

[2] A voracious reader, Lederberg would likely have gotten to Ledley's article in any event.

Fig. 1. Robert Ledley at the control console of the first whole-body CAT scanner, Georgetown University, circa 1974.

at least 8 books. There is almost no major subdiscipline in biomedical computing that he has not dipped into, though he has had particularly strong interests in medical imaging issues. His work has embraced both software and hardware engineering. He had a long and productive friendship and collaboration with Margaret Dayhoff [1925–1983] [8], a seminal figure in the field that was to become known as bioinformatics, who was based at NBRF, and originated the *Protein Information Resource* (PIR) and *The Atlas of Protein Sequence and Structure* [1965–1978], the immediate progenitor of *GenBank*.

The most widely known of Ledley's achievements is likely his construction of the first operational whole-body CAT scanner, ACTA, in 1973. Ledley shared some entertaining anecdotes about this period of his life in an interview in 2005, revealing that the initial impetus arose from sudden NIH grant funding cutbacks under President Nixon [9]. He founded a company to manufacture this device, operating it on a shoestring, without the benefit of venture capital. Fig. 1 shows a beaming Ledley sitting at the control console of this pioneering diagnostic machine, which now resides in the Smithsonian Institution's National Museum of American History.

If the photos on the walls of Ledley's office are any indication, pride of place among his numerous awards goes to the National Medal of Technology. Presented to him in 1997 by President Clinton, it cited his pioneering contributions, including his work on CAT scanning and chromosome analysis. A telling anecdote about Ledley's pluck and determination to get things right: when the official photographs from the evening awards presentation turned out poorly, Ledley simply called up the White House; to his credit, the President was happy to schedule a re-presentation in the Oval Office (Fig. 2).

Robert Ledley's legacy lives on in the field he helped to create, and most particularly in this journal. Thanks for all you have given us, Robert, and for the example of a purposeful and passionate professional life, well and fully lived. In the months ahead, this journal's Editorial Board, aided by the counsel of respected scientists from diverse fields, will be pondering ways in which to best position this publication to carry on with vigor and impact into its next 40 years. That will be the best tribute we can pay.

Fig. 2. President William Jefferson Clinton re-presenting the National Medal of Technology to Robert Steven Ledley in the Oval Office of the White House in 1997.

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