Ernest Beutler (1928–2008)

In the 80 years and five days of his life, my father, Ernest Beutler, was many things to many people. A celebrated academic hematologist to some; a personal physician to many; a distinguished scientist to others; a teacher to still others. A writer of software. A father and grandfather; a husband; a brother. It is difficult to recount his life, rich and fulfilling as it was, within the space of a few pages. But the highlights and central currents of his story may be told.

He was born during the waning years of the Weimar Republic, in Berlin, Germany, on September 30, 1928. Both of his parents (Alfred David Beutler and Kaethe Beutler, née Italiener) were physicians and both were Jews. The second of three children, he was preceded by an older brother, Frederick, born in 1926, who later became a professor of mathematics at the University of Michigan, and followed by a younger sister, Ruth, born in 1932, who later became a clinical psychologist and died in 1993.

His father was an internist with a particular interest in electrocardiography. His mother, a pediatrician, was in pre-war times the physician to the children of Magda Quandt née Rietschel, later Magda Goebbels, wife of the German propaganda minister. This particular point is recalled to emphasize that the family was perhaps as "integrated" into mainstream life as Jewish families could become in pre-war Germany. Yet his mother averred many years later that she had never felt herself an accepted member of German society. And she became acutely uncomfortable as the Nazis gained political power. In 1935, when he was seven years of age, the family emigrated to the United States, escaping the disaster that would otherwise have overtaken them.

His mother was the prime mover in the decision to leave Germany. It was not that she foresaw the murder of the Jews of Europe that would soon take place, but rather, that she was indignant at the progressive annulment of their rights, and saw that her children would be denied an education. The family's departure was tense, because she had contracted with an illegal agency to try to salvage some few thousand German marks, as all of their property was to be confiscated. She was therefore fearful of being arrested by the Gestapo at the border. But they left Germany without incident and crossed the Atlantic on the Aquitania, sister ship of the better-known Lusitania. My father and his family settled in Milwaukee, Wisconsin.

A child with an immigrant's mindset and a will to do well in life, my father spent only about eight years in Milwaukee. He remembered his first day in school after arriving in America, speaking almost no English. When the teacher instructed his class to do something that he didn't understand, he copied the paper of the child next to him, only to find that what the teacher had said was "write your name." But he soon excelled in school, and his outstanding academic performance earned him a place in a special program at the University of Chicago, initiated by Robert Maynard Hutchins, then President of the University, whereby he could complete his undergraduate and medical training in only six years. He graduated from medical school at the age of 21, the valedictorian of his class. On June 15, 1950, the day before his graduation from medical school, he married my mother (Brondelle, or Bonnie), remaining married to her until his death 58 years later. This led to the birth of four children (Steven, Earl, myself, and Deborah) and, so far, 9 grandchildren, 8 of whom are still living.

Concurrently, he built a career that was amazingly broad in its scope. He took pride in the sheer diversity of his accomplishments over the years, deploring the fact that some of his former trainees were still working on the same topics they had pursued in his lab 25 years earlier. People who profess expertise in many fields are not often taken very seriously. But my father was one of those few, extraordinary people with the ability to do well at many different things, and he made outstanding advances in many different areas of research. He generally kept several balls in the air at one time. Efficiency, multi-tasking, optimal use of time and resources were extremely important to him, in work and in personal life alike.

Spurning the conventional wisdom that one ought to be either a scientist or a clinician but not both, he became both. And in both he excelled, felt exceptionally confident, and understood the "big picture." Moreover, his list of interests included many items set apart from science and medicine. He taught himself to write code, and programmed computers from mid-life

onward, using them to speed progress in his own laboratory and as the basis of the first commercial bibliographic retrieval system, described in more detail below. He was fascinated by the stock market, options, commodities and currencies, and over the years, he managed his finances extremely well. But he mainly liked being able to test his theories, opinions and judgment in real time and trading on the market was a way for him to do so. His was a restless intellect. And he tended toward skepticism; even toward a contrarian stance, in both his professional and private life. He was not one to accept pronouncements without proof, and believed that questions susceptible to logic ought never to be settled by consensus.

Some of his most brilliant and enduring biomedical discoveries were made during his earliest years of research. After graduating from medical school he stayed on at the University of Chicago and completed his residency in 1953. He then applied for a commission as a Lieutenant in the U.S. Army, and was assigned to the Army Malaria Research Program. During this period, he worked at Joliet Prison in Illinois (1953-1954), investigating the hemolytic anemia occasionally produced by antimalarial drugs. His technicians at that time were convicted felons. He later explained that this taught him how to evaluate data for internal consistency. But interestingly, he also reported that for the most part, the prison inmates were extremely reliable and trustworthy in their work. In the course of his studies at Joliet, he identified glucose-6-phosphate dehydrogenase (G6PD) deficiency as a genetic defect that leads to the lysis of red blood cells under conditions of oxidative stress. This hinged on his demonstration that red blood cell glutathione was unstable to oxidative stress. Later, he was to develop an assay for glutathione that was widely used in studies of red cell oxidative metabolism. And his understanding of glutathione stability set the stage for an extraordinary discovery.

After his military service was complete, he joined the faculty of the Department of Medicine at the University of Chicago, and continued his studies of red blood cell and iron metabolism. In 1959, he left Chicago to become Chairman of the Department of Medicine of the City of Hope National Medical Center in Duarte, CA. There he flourished, unhindered by the fact that the City of Hope was then rather obscure. Indeed, he brought intellectual rigor to the institution and helped to put it on the map. Two years into his stay in California, he made what he certainly considered his most important contribution to science.

A colleague – and ultimately a life-long friend of my father's – Susumu Ohno came to the City of Hope only a short time before my father did. There, he demonstrated that the histologically observable Barr body in the nuclei of mammalian female cells was a heterochromatic X chromosome. My father quickly recognized that this might account for the variable expression of X-linked genes in females heterozygous for X-linked mutations. He soon determined that random X chromosome inactivation causes tissue mosaicism in female mammals, in that each somatic cell expresses one (but not both) of the alleles of X-linked genes with which it is endowed. This he accomplished by demonstrating that two populations of erythrocytes exist in the blood of African American women who are heterozygous for G6PD deficiency: those with normal levels of enzyme and those with deficient levels of enzyme. Mary F. Lyon independently hypothesized that variegated coat colors in mice might arise from random X chromosome inactivation. Her work was also based upon Ohno's observations.

X inactivation was the first example of stochastic epigenetic silencing of genes in mammals: a key means by which the genome governs the expression of its many genes, in situations ranging from development to cancer to adaptation to environmental change. It had vast implications, some of which remain to be fully explored even today. It was a discovery that many might dwell upon for years. But my father had many other interests as well, and he was eclectic in following them.

His early work on G6PD deficiency led him not only to the X-inactivation hypothesis, but also to explore hemolytic anemias caused by many other enzyme deficiencies. The systematic methodology that he developed became the standard approach to study of patients with these disorders. He also made major contributions to the understanding of Tay-Sachs and Sandhoff's diseases. He purified the protein that is aberrant in both diseases and demonstrated its heteromeric structure. His group cloned the gene responsible for Gaucher's disease, and explored treatments for this disease as well as diagnostic tests for its presence. He developed a screening test for galactosemia, which is used to this day to detect the disease in neonates, and prevent its severe consequences. He designed the first artificial storage media for red blood cells, introduced the use of mannitol (still a mainstay in red cell preservation), devised a variety of approaches to maintaining red cell ATP and 2,3-DPG levels, and determined the viability of stored cells in human volunteers.

During the 1970s, he developed a bone marrow transplantation program to treat patients with hematologic malignancies. This program, guided by Dr. Karl Blume, had an outstanding track record and was mostly self-supporting, but my father was deeply upset at the time by the lack of administrative support for what he correctly perceived as a pioneering medical technology. Largely for this reason, he decided to leave City of Hope, and in 1979 was recruited as the Chairman of the Department of Basic and Clinical Research at the Scripps Clinic and Research Foundation. Three years later, he became Chairman of a merged department (the Department of Molecular and Experimental Medicine) at Scripps, which later became The Scripps Research Institute in La Jolla, CA. He maintained this position until his 80th birthday, by which time he was very ill.

After moving to La Jolla, my father developed a new bone marrow transplantation unit and Clinical Research Center, ironically set up in the same ward in which he himself later died of a mantle cell lymphoma. Together with Dennis Carson, he developed 2-chorodeoxyadenosine for the treatment of chronic

leukemias and lymphomas. With Jack Sipe, he explored the use of 2-CDA in multiple sclerosis as well: a disease of particular interest to him because his sister suffered and died from it. And before his own death, he was himself treated with this drug, tragically with little or no response.

Unlike many biologists of his generation, my father was not shy to adopt the tools of molecular biology when the cloning revolution occurred. He and his group cloned cDNAs, searched for mutations, and even made a foray into positional cloning. Beginning in the mid-1990s, when nearly 70, he attempted to positionally clone the mutation responsible for the adult-onset form of hereditary hemochromatosis. He failed to identify the mutation before it was found by others to affect HFE, a member of the major histocompatibility complex family of proteins. However, in contrast to the reports of others, he found that only about 2% of males and no females homozygous for the mutation showed severe clinical manifestations of the disease. This study depended upon genotypic and phenotypic analysis of more than 43,000 subjects, and upon an archive of DNA samples from carefully phenotyped human beings that he himself initiated.

Hematology was my father's center of gravity, and the American Society of Hematology was something of an extended family to him. He served as an editor of Williams Hematology, a widely used text in hematology, since its inception (its first edition was printed in 1972), and was sometimes the lead editor. And he published more than 800 papers over the course of his life.

In this, as in almost all of his endeavors, he was helped by an excellent ability to write. This was perhaps all the more remarkable since English was not his first language. And as a prolific writer, he longed for – and saw the potential for – a computerized bibliographic retrieval system to be used in writing scientific papers. While at the City of Hope, he began to use a system of marginally punched cards to organize his references, but with thousands of these cards, it soon became unwieldy. In the early 1970s, the City of Hope had purchased a PDP-11 computer for the clinical laboratory, and he was able to get some time from a talented programmer named Dean Campbell who wrote a rudimentary system for entry and retrieval of references, and also the creation of bibliographies. He was proud of this system, and demonstrated it to all his colleagues, most of whom expressed admiration and strong interest in the program; my father offered to give it to them, but all declined, since it required the purchase of a $200,000 computer system.

In the early 1980s, with the advent of personal computers (but well before the release of the first IBM PC), he decided that it would be practical to develop a bibliographic management software package that could also be offered commercially. Since my brother, Earl, had gone into the software field and had just sold his first business, my father suggested that they form a company and write the program as a family project. They did so in 1982, creating Research Information Systems (RIS), and since Earl did not seem to make this project a high priority, my father learned CB86 BASIC and wrote the program himself, with some assistance from Earl. It was released commercially in 1983 as Reference Manager Version 2 (he took a page from Apple and decided that Version 1 sounded immature), and was the first program of its type. He continued to develop the program for a year or two, fixing bugs and releasing new versions every few days. Earl went on to run RIS, and the two later developed Reference Update, which was the first successful diskette-based current awareness service, taking a significant market share from the then ubiquitous Current Contents.

My father was honored in many ways during his career. He received the prestigious Gairdner Award in 1975, and was also elected to the American Academy of Arts and Sciences during that year; then to the National Academy of Sciences in 1976, and later, to the Institute of Medicine. He was indeed a "Renaissance Man," and perhaps one of the last of these. He left his mark in many areas of science, nowhere more so than in hematology. No serious student of hematology will fail to encounter his work, now or in the future.

There is much more that could be told. He loved classical music (particularly Mozart; almost equally Bach). He had a tremendous sense of humor. He was a temperate and pragmatic person who rarely got angry, and never stayed angry for long. He was insightful and empathetic. He was faultlessly honest. And he loved his family. We who knew him well remember him as a good and great man. We grieve that he is gone. We must also count ourselves as lucky to have known him.

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