A Biographical Memoir by
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ERNEST BEUTLER

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BY MARSHALL A. LICHTMAN

ERNEST BEUTLER was among the most influential and productive medical scientists of the second half of the 20th and the first decade of the 21st centuries. A practicing physician throughout his 54-year research career, he contributed to improvements in diagnostic tests, treatment, and our understanding of the pathogenesis of hematological disorders, including inherited and acquired anemias; red cell enzyme abnormalities, notably glucose-6-phosphate dehydrogenase deficiency; iron deficiency; and inherited iron overload disorders (e.g., hemochromatosis); the glycolipid (lysosomal) storage diseases, especially Gaucher disease; and several types of leukemia. He had a broad interest in biomedical science and an ability to make important, often seminal contributions to the understanding or therapy of a diverse array of medical abnormalities.
Beutler encouraged his students to pick important biomedical problems. He was not disappointed when his former trainees continued to work on a similar problem for long periods—it was more a matter of advancing the depth of the questions they were asking and the techniques they were applying. He pursued similar topics throughout his career but progressively advanced his approaches from those appropriate to the 1950s to those appropriate to the 21st century, notably investigating the biochemical or genetic basis of diseases of his interest. Despite the sophistication of his scientific approaches, his simultaneous function as a physician caring for patients gave him the insight and opportunity to launch studies that advanced therapy, notably for iron deficiency or iron overload, acute myelogenous leukemia, hairy cell leukemia, and Gaucher disease.

Beutler’s decades-long contributions to the understanding of red cell enzyme disorders, lysosomal storage diseases, disorders of iron metabolism, blood cell transfusion practices, and other areas of his interest provided a role model for his protégés: continue to dig deeper, adopt advanced techniques, supersede conventional wisdom, and provide new insights. He cautioned about making the assumption that our understanding of biomedical processes was profound and that what was left for scientists was to fill in the gaps. He argued that much fundamental biomedical knowledge was undiscovered and awaiting to be illuminated by the prepared mind of the industrious young scientist. He preferred a small research team, often himself and one or two skilled and experienced technologists, not the megalaboratory with junior faculty and dozens of pre- and postdoctoral fellows.
This approach kept him more closely involved with the research in his laboratory and avoided erroneous or uninspiring surrogate research in which the responsible senior scientist was not deeply and carefully involved in the planning and interpretation of experiments. It also fit with his preference for independent work and independent thought.

Beutler was highly organized and efficient and was a pioneer in applying computer techniques to his work in innovative ways. As an example, he devised, programmed, and made available to the scientific community the first electronic bibliographic software, which he later made commercially available under the title “Reference Manager.” He was consulted by scientists around the world because of his knowledge and his accessibility. His scientific writing was graceful and concise, despite English being his second language. He was innovative in all that he did, looking for new and better ways to approach older, less-efficient processes. He had a wonderful, gentle wit and a judicious temperament and was gracious and helpful to his colleagues. He was a person who valued the truth, even if it was uncomfortable.

EARLY LIFE, FAMILY, EDUCATION, AND ENTRANCE INTO MEDICINE (1928-1952)

Ernest (né Ernst) Beutler was born in Berlin, Germany, at the time of the last throes of the Weimar Republic, to Alfred and Kaethe (née Italiener) Beutler, both physicians. His father was an internist interested in electrocardiography and his mother a pediatrician who assisted in the development of infant formulas at a time when wet nursing was de rigueur. Beutler had an older
was largely responsible for the move of the family to the United States. Beutler quickly learned English and eventually attended Shorewood High School.

At age 15, after two years of high school, Beutler entered the University of Chicago as part of an innovative and controversial program established by Robert Maynard Hutchins, then president of that university. He completed his baccalaureate degree in two years at age 17. He accomplished this by achieving credit for a course by passing a six-hour comprehensive examination in lieu of taking the course, an accepted part of the program. He also took extra courses so as to complete the credits required for his degree more quickly. Beutler completed his medical doctorate degree at the University of Chicago and received his internal medicine residency training at the University of Wisconsin.

In 1935 at age seven Ernest Beutler and his family, after first considering Palestine as a site for refuge, immigrated to Milwaukee, Wisconsin, escaping the approaching terror to be inflicted on European Jews by the National Socialist (Nazi) Party under the rule of Adolph Hitler. His mother, recognizing the progressive limitations on the rights and opportunities for Jews in Germany,
of Chicago Hospitals. His doctor of medicine degree was bestowed at age 21, and he was the valedictorian of his class. He described having an interest in science from childhood and he credited the stories of scientists examining the nature of the infectious diseases in the book *Microbe Hunters* as contributing to an early interest in medicine.

On June 15, 1950, upon completion of his medical school studies, he married Brondelle May (“Bonnie”) Fleisher. They had four children: Steven Merrill, a physician and infectious disease specialist practicing medicine in Redlands, California; Earl Bryan, a software developer and businessman in San Diego; Bruce Alan, a physician-scientist and director of a genetics program at Scripps Research Institute in La Jolla, who shared the Nobel Prize in Physiology or Medicine in 2011 for his studies of innate immunity; and Deborah Ann, an internist in Pasadena. Bruce Beutler has since moved to Southwestern Medical Center in Dallas, where he is Regental Professor and director, Center for Genetics of Host Defense.

Bonnie and Ernest Beutler remained married for 58 years until Beutler’s death from mantle cell lymphoma in 2008. He remained active in his research laboratory until a few weeks before his death. Indeed, he tracked the effects of his therapy by using polymerase chain reaction studies to determine the residual size of his lymphoma cell population following each chemotherapy cycle.

**BEGINNING RESEARCH IN HEMATOLOGY AND MILITARY SERVICE (1953-1959)**

During his second year of medical residency at the University
of Chicago, Beutler spent two months in the hematology division, and he was motivated to consider diseases of blood cells as a career interest because of the impact of his mentors. During his third year of postdoctoral clinical training, he focused on clinical hematology. Leon Jacobson, who was head of the hematology division and later became chair of medicine and dean of the medical school (and was elected to the National Academy of Sciences in 1965), had a notable influence on Beutler’s developing interests in hematology. Jacobson was interested in radiobiology as well as hematology, and Beutler published his first paper, in 1954, with Jacobson on the effect of irradiation on the mitotic cycle of *Escherichia coli* (Beutler et al., 1954d). He also published his second paper on the histologic findings of the liver and bone marrow in iron deficiency with another mentor in hematology at Chicago, Matthew Block (Beutler et al., 1954c). This paper initiated an interest in iron metabolism and its disorders that extended throughout his scientific career. Beutler’s later contributions to our understanding of the pathogenesis, manifestations, and treatment of iron deficiency anemia and iron overload disorders were singular (Beutler, 2010).

It was common for medical residents to choose their career pathway based on the influence of a mentor with whom they worked closely and whom they respected. Beutler (with many others who chose hematology as a medical specialty) was attracted to the field by the ability to make a diagnosis based on one’s own examination of the patient’s blood counts, blood film, and sometimes the marrow cells. These tests were performed and interpreted by the attending hematologist, not requiring the
involvement of others. This clinical approach appealed to his sense of independence and self-reliance and was a notable feature of the discipline of hematology. At that time few sophisticated techniques—such as cell flow analysis, reliable enzyme assays, cytogenetics, immunochemical tests, and the polymerase chain reaction—were available.

After completing his residency in 1953, Beutler volunteered for the U.S. Army Medical Corps at the time of the Korean War. American troops in Korea were suffering a high rate of malarial infection, necessitating better prophylaxis and treatment of that disease. Lieutenant Beutler was assigned to the Army Malaria Research Program, a collaboration between the U.S. Army and the Department of Medicine at the University of Chicago. The research in which Beutler was involved was conducted on informative inmates of African descent at the Statesville, Illinois, penitentiary near the town of Joliet. They volunteered to participate. Beutler was part of a small team of scientists from the University of Chicago who, jointly with the Army Medical Corps, were examining why a subset of men of African descent given the principal prophylactic and therapeutic antimalarial, primidine, developed an acute hemolytic anemia two days after ingestion, making the use of primidine problematic in a large segment of the troops in Korea.

From 1954 to 1957 Beutler and his colleagues at the University of Chicago, notably Ray Dern, published a classic series of experiments defining the nature of the hemolytic anemia in primaquine-sensitive persons (Dern et al., 1954, 1955; Beutler et al., 1954a,b; Beutler et al., 1955a,b). They
determined that the primiquine sensitivity was intrinsic to the red cell (inherited) and affected red cells that were more than 60 days old (red cells have a finite lifespan of approximately 120 days). Thus, after a brisk hemolytic event, continued administration of primiquine resulted in a steady-state mild hemolytic anemia, the result of a compensatory increase in red cell production and a very slow hemolytic rate from the small proportion of residual red cells that age to susceptibility each day. Beutler highlighted the effects of primiquine in a classic review article in 1959 (Beutler, 1959).

During these studies, Beutler developed an assay for red cell glutathione stability (Beutler, 1957) and showed that the red cells from primiquine-sensitive individuals, whether exposed in vivo to primiquine or in vitro to acetylphenylhydrazine, had a marked decrease in glutathione, localizing the problem to the pentose phosphate pathway in the red cell (Beutler et al., 1957). The early studies of primiquine-sensitive persons provided the focus for the discovery by others that glucose-6-phosphate dehydrogenase (G6PD) was the enzyme deficient in the red cells of affected individuals. It was later determined by family studies that the enzyme was inherited as a sex-linked trait, indicating that the gene that encoded the enzyme was on the X chromosome. The identification of a specific X-linked genetic defect, hemizygosity for G6PD deficiency A-allele, in the late 1950s was important in part because it explained the nature of one of the world's most prevalent inherited abnormalities and provided a quintessential example of the interaction of genetics and environment. The phenotype of inherited
G6PD deficiency was dependent on exposure to drug or infection-induced oxidative stress on the red cell. The reducing capability in the red cell is the result of the generation of protons in the pentose phosphate pathway, in turn dependent on the activity of G6PD.

Beutler’s continuous research in the field over 54 years resulted in his becoming a leading authority on G6PD deficiency (Beutler, 1969, 2008). He also was a member of a working group studying the impact of the red cell enzyme deficiency on the design of new antimalarial drugs (Beutler et al., 2007). One of his last publications dealt with G6PD deficiency worldwide and was published by his collaborators posthumously in 2009 (Nkhoma et al., 2009).

Following completion of Beutler’s assignment to the Malaria Research Project he was transferred to Camp Detrick, Maryland, where he worked in the biological warfare program. He was discharged in 1955 at the rank of captain and returned to the University of Chicago as a member of the faculty in the department of medicine and the hematology division. He continued his studies of red cell disorders and iron metabolism and increasingly gained stature as a research and clinical hematologist.

**THE YEARS AT CITY OF HOPE (1959-1979)**

Beutler’s rapid rise to prominence resulted in his being offered the chair of the department of medicine at City of Hope National Medical Center in Duarte, California in 1959. He had become increasingly constrained by the lack of the opportunity to increase the size of his program at Chicago, and he saw this
move as a chance to expand his research program. Despite advice to the contrary by his mentors, he accepted the position at City of Hope. Although others saw him as taking a dangerous step in going to a scientific institution that was neither part of a university nor considered preeminent, his visits to City of Hope led him to believe that he could thrive in that environment and he was excited about building a research and research training program that he could design and execute himself. At age 31, not having run a program approaching these dimensions, he left the University of Chicago for City of Hope and remained there for the next 19 years.

During his tenure at City of Hope Beutler expanded his studies of inherited hemolytic anemia resulting from enzyme deficiency. He developed assays for the enzymes in the glycolytic and pentose phosphate pathway in red cells and in 1971 published an important monograph on the techniques of measurement of the red cell enzymes and metabolic intermediates (Beutler, 1971); a second edition was published in 1975. His laboratory became a resource for hematologists throughout the country and abroad who had unexplained cases of hemolytic anemia and were trying to determine if they represented inherited red cell enzyme disorders; for example, from 1980 to 1987 over 700 samples were sent to his laboratory at City of Hope, from which he was able to diagnose 82 cases of inherited hemolytic anemia from seven different red cell enzyme deficiencies (Hirono et al., 1988). He thus became one of the leading authorities on inherited hemolytic anemia resulting from an enzyme deficiency (Beutler, 2006a).
Beutler had been perplexed by the variability in the susceptibility to hemolysis among women who carried one copy of the mutant gene for G6PD deficiency. Unlike hemizygous men in whom all red cells were enzyme deficient, women who inherited the mutant X-linked gene from one parent would have only half of their red cells affected and would be expected to have a milder effect from a provocative exogenous exposure such as a relevant drug, infection, or ingestion of fava beans. The exceptions to this pattern perplexed Beutler.

When Beutler moved to City of Hope, he was unaware that Susumu Ohno, a geneticist who was doing pioneering research on the sex chromosomes was working in another department at that institution. In 1959 Ohno had reported that the condensed chromatin evident in the interphase cells of the mammalian female, described by Murray Barr and Ewart Bertram in 1949 as the sex chromatin and later referred to as the Barr body, was a heterochromatic X chromosome, implying that its genes were not transcribing. It was later shown that epigenetic silencing of most of either the maternal or paternal X chromosome occurred randomly early in embryogenesis and resulted in a balance of gene dosage in the mammalian female with two X chromosomes compared to the male with one. Beutler was encouraged to seek out Ohno by his friend and colleague Arno Motulsky (b. 1923), a geneticist and hematologist at the University of Washington, when they were together at the VIII International Congress of Hematology in Tokyo in September 1960.

Motulsky thought that Ohno would be helpful in questions
related to the genetics of G6PD deficiency, since G6PD was encoded by an X-chromosome-linked gene. Motulsky and Beutler, although at different institutions, were friends and colleagues since both were interested in genetics and hematology and both had escaped Nazi Germany. In those days American academic medical specialty societies were small and intimate and most members knew one another. Motulsky’s suggestion that Beutler seek out Ohno had a profound effect on Beutler’s research and Ohno and his wife, Midori, and Beutler and his wife, Bonnie, became lifelong friends. Beutler later credited Ohno with being the “father of [the idea of] X chromosome inactivation.”

In 1962 Beutler published a landmark paper entitled “The Normal Human Female as a Mosaic of X-Chromosome Activity: Studies Using the Gene for G6PD Deficiency as a Marker” (Beutler et al., 1962). The authorship included his technologist Mary Yeh and Virgil Fairbanks (b. 1930), the latter a clinical research associate in Beutler’s laboratory and now emeritus professor of medicine, laboratory medicine and pathology at the Mayo School of Medicine and consultant at the Mayo Foundation Clinic. Beutler had been contacted by William Valentine (b. 1917), an expert in hemolytic anemias, chief of hematology, and later chair of medicine at the University of California, Los Angeles. In 1961 Valentine was asked to see a Sephardic Jewish woman who lived in North Hollywood who had recurrent episodes of severe hemolysis, requiring transfusion. Valentine quickly identified the basis of the problem; she ate fava beans. She was diagnosed with fava-induced acute hemolytic anemia,
known by then to be related to a red cell deficiency in G6PD. Beutler and Valentine were friends and colleagues, and Valentine knew of Beutler’s interests in G6PD deficiency. Valentine contacted Beutler to suggest he study this patient and her family. In a letter to the journal *Lancet* in 1961 Beutler and his coworkers described the family pedigree and ascertained that despite the unexpected complete absence of G6PD activity in the red cells of the propositus, it was not possible for her to be homozygous for G6PD deficiency because she had two sons with normal red cell G6PD levels. She also had a sex chromatin body in her buccal mucosal cells and a normal karyotype. Beutler puzzled as to how the propositus, a woman and heterozygote, could be totally deficient in red cell G6PD. Beutler ultimately realized, based on his developing an understanding of random X-chromosome inactivation in the female, that inactivation would be expected to inactivate either the maternally or paternally derived X chromosome in tissue cells half the time. He realized that an explanation for these findings was that the X chromosome with the normal allele for G6PD in the woman he reported had been inactivated in all her red cell precursors, not in half, leaving the expression of only the mutant gene on the alternative X chromosome. Beutler reasoned that, as determined by the Poisson distribution, rarely the “random” inactivation could be in a markedly skewed ratio, in this case approximating 100:0, normal to mutant X chromosome, resulting in exaggerated expression of the mutant G6PD gene and complete enzyme deficiency and marked susceptibility to hemolysis in a female.

No one, however, had yet established that women were
mosaics for X-chromosome-linked genes. Whereas mice have an X-chromosome-linked gene that determines pigmentation (coat coloration) that can be used in such studies, as was done simultaneously by Mary Lyon, such studies were not possible in women. Beutler considered red cell G6PD an ideal test system by which to evaluate the hypothesis that the human female represents a genetic mosaic. Published in the Proceedings of the National Academy of Sciences, the paper presented a series of experiments designed to determine the kinetics of red cell G6PD enzyme activity in women heterozygous for the gene (Beutler et al., 1962).

Consistent with his hypothesis Beutler was able to demonstrate that women heterozygous for G6PD deficiency have two distinct erythrocyte populations, one with normal enzyme activity (active X chromosome without mutation expressing G6PD in an average of half of the erythroid progenitor population) and the other with absent enzyme activity (active X chromosome carrying mutation failing to express G6PD in half of the erythroid population). This report was the first of Beutler’s 39 papers published in the Proceedings of the National Academy of Sciences.

G6PD catalyzes the first enzymatic step in the pentose phosphate pathway, transforming glucose-6-phosphate to 6-phosphogluconic acid, generating reduced nicotinamide adenine dinucleotide phosphate (NADPH), which must be generated in order to maintain a supply of reduced glutathione in the red cell. In the absence of appropriate reducing capacity, sulfhydryl groups in red cell enzymes and the red cell membrane undergo damaging oxidation and hemoglobin function is compromised. Beutler and
colleagues showed that when incubated with the oxidizing agent acetylphenylhydrazine, the rate of decline in glutathione in the blood of females heterozygous for the G6PD gene approximated that of an artificial equal mixture of type-compatible blood from a normal subject and from a G6PD-deficient male. Both samples tested generated a two-component curve, with a sharp inflection in red cell glutathione between the first and second components. This result—as opposed to the generation of “a single curve of intermediate slope” when assaying the blood of G6PD heterozygous females—would be expected if these subjects had a single population of erythrocytes with intermediate enzyme activity. This finding strongly supported the concept of two distinct red cell populations in these subjects, one with an active and one with an inactive X chromosome in their erythroid precursor cells.

Beutler’s laboratory provided further evidence in support of this concept by measuring the rate of reduction of methemoglobin in nitrite-treated red cells in the presence of Nile blue sulfate. Nile blue sulfate reduces methemoglobin; its ability to do so is linked to the availability of the end products of the pentose-phosphate shunt and is therefore dependent on G6PD activity. As predicted, the rate of reduction of methemoglobin in a sample that consisted of an artificial mixture of erythrocytes from a G6PD deficient male with those from a normal subject as well as in a sample from a female heterozygous for G6PD deficiency displayed a two-component curve.

Beutler and his research associate Virgil Fairbanks designed a quick and simple method for
detecting G6PD deficiency based on the reduction of a tetrazolium dye, which turns purple in the reduced state. For several years there was a commercially available kit for G6PD deficiency screening using this method. Subsequently Beutler developed a screening test based on the fluorescence of NADPH in ultraviolet light. NADP does not fluoresce. G6PD reduces NADP to NADPH, which exhibits strong fluorescence in ultraviolet light.

In a presentation given at the IX Congress of the International Society of Hematology in September 1964 in Mexico City, Beutler summarized his earlier observations concerning G6PD as a marker of X-chromosome mosaicism. He discussed the contributions of Ohno to their work, crediting him with making the astute observation that one of the X chromosomes of mammalian females is hyperchromatic, producing the sex chromatin in the interphase nucleus of female cells in mammals. In his presentation Beutler stated, “These findings suggested independently to us and to Mary Lyon in England that perhaps only one X chromosome could be active in directing protein synthesis.” They elaborated upon their hypothesis that the human female is a genetic mosaic in that she has two populations of cells, one of which has an active maternal X chromosome and another with an active paternal X chromosome. The statement that Beutler made was in agreement with the hypothesis proposed by Lyon:

We should like to propose that when the egg is fertilized by an X-chromosome-bearing sperm, both X-chromosomes remain active for a number of divisions. At the morula stage of embryonic devel-
opment, the Barr body appears. We would suggest that at this stage of development the non-homologous portion of the X-chromosome is inactivated, at least partially. We would propose that inactivation of X-chromosomes takes place at random, the maternally-derived X-chromosome being inactivated in some cells, the paternally derived X-chromosomes being inactivated in other cells. From this stage on only one X-chromosome is active in directing protein synthesis in each cell and this is the only active X-chromosome in the entire clone of cells produced from this precursor cell. Thus, the normal human female may be considered to be a mosaic of clones of cells, some containing an active maternally-derived X-chromosome, others containing an active paternally-derived X-chromosome... The hypothesis that Dr. Lyon and we have proposed appears to us to explain most satisfactorily the lack of dosage effect and the marked variation and expression of heterozygotes for glucose-6-phosphate dehydrogenase deficiency and other sex-linked traits. While it must be admitted that the evidence that we have obtained that there are two red cell populations in heterozygotes for G-6-PD deficiency is indirect, we have found no experimental situation in which the cells of heterozygote G-6-PD deficiency behave differently than an artificial mixture of mutant and normal erythrocytes.”

Mary Lyon published her hypothesis based on her insights and studies on coat color in mutant mice in the April 22, 1961, issue of *Nature* (190:372-373). Beutler, Yeh, and Fairbanks’s work was transmitted to the *Proceedings of the National Academy of Sciences* on November 30, 1961 by Alfred Sturtevant (1891-1970), then at the California Institute of Technology, and was published in January 1962. (Forty years earlier Sturtevant had been a student in Thomas Hunt Morgan’s “Fly Lab” at Columbia University where the
first sex-linked trait, red eye color in *Drosophila melanogaster* was discovered.) Beutler had been unaware of the earlier paper published by Lyon based on the distribution of coat color in informative mice when he considered G6PD an ideal marker to study X-chromosome inactivation in women.

During his time at City of Hope, Beutler developed a test for galactosemia, an inherited, highly morbid and fatal disorder, to screen infants for the disease so that appropriate dietary preventive measures could be instituted. Taking advantage of the fact that the enzyme deficiency that causes galactosemia is expressed in red cells, Beutler developed a test that has been used to screen potential carriers and newborns for the disease (Beutler and Baluda, 1966; Beutler et al., 1967). He discovered a prevalent enzyme variant that he dubbed the Duarte variant (Beutler, 1991). He later used DNA testing to determine the prevalence of the disorder (Suzuki et al., 2001). He wrote 24 papers on the biochemistry and diagnosis of galactosemia over nearly four decades of study.

Beutler had a careerlong interest in blood cell storage and transfusion and published several important papers in the field (Beutler and Duron, 1966; Chillon et al., 1977). A noteworthy contribution was his discovery that the addition of mannitol to units of packed red cells decreased in vitro hemolysis and prolonged their shelf life. The additive is still in use, and given the number of units of packed red cells transfused and the difficulty of meeting blood needs from donations, the prolongation of shelf life is an important contribution to medical therapeutics.

In 1970 increasing evidence
that allogeneic hematopoietic stem cell transplantation was going to be a useful and important modality for treating hematologic malignancies—based on the pioneering work of E. Donnall (“Don”) Thomas (b. 1920) in Cooperstown, New York, and then Seattle, Washington—prompted Beutler to start a marrow transplantation program at the City of Hope. Thomas and Beutler were friends and colleagues and were members of the American Society of Hematology. Thomas shared the Nobel Prize in Physiology or Medicine in 1990 for his development of allogeneic hematopoietic stem cell transplantation. Beutler recruited Karl Blume, a former research fellow studying red cell biochemistry with him, to direct the program. Blume returned to Duarte from Freiburg where, with Beutler’s support, a new major center in transplantation was
developed. Blume and Beutler published the first paper supporting the use of allogeneic marrow cell transplantation as a primary treatment of acute leukemia in first remission (Beutler et al., 1979). Blume later became the director of the hematopoietic transplantation program at Stanford Medical Center.

At City of Hope Beutler also began a series of studies of lysosomal storage diseases, notably Tay-Sachs and Gaucher diseases. He purified glucocerebrosidase, the enzyme deficient in Gaucher disease, from human placenta and showed its infusion was safe and produced some evidence of improvement in a patient so treated (Beutler and Kuhl, 1970; Dale and Beutler, 1976). He continued what was to be his singular contributions to this field after he left City of Hope (see below).

THE YEARS AT SCRIPPS CLINIC AND RESEARCH FOUNDATION (1979-2008)

In 1979 the City of Hope Medical Center was discussing closing their marrow transplantation program and Beutler became concerned about the support for one of his most important clinical programs. He was by this time recognized as one of the most productive hematologists in the country and had many opportunities to move to another venue to continue his work. In 1979 Beutler accepted the chair of the Department of Clinical Research at the Scripps Clinic and Research Foundation and became senior hematologist in the Scripps Clinic. He was subsequently given responsibility for two other programs at Scripps, later combined, under his direction, to form the Department of Experimental and Molecular Medicine. The foundation was
renamed the Scripps Research Institute.

At Scripps he established a hematopoietic stem cell transplantation program now entering its fourth decade of service. Beutler also continued his broad interests, including the lysosomal storage diseases, especially Gaucher disease. He embraced molecular cloning and together with Joe Sorge, a postdoctoral fellow in his laboratory, isolated the glucocerebrosidase cDNA and the gene (Sorge et al., 1985). The first effective enzyme replacement therapy for Gaucher disease, glucocerebrosidase (Cerezyme®), was made from the cDNA Beutler provided the company manufacturing the drug. He also identified several new Gaucher disease mutations. He showed that the dose of glucocerebroside recommended by the company was unnecessarily high and unnecessarily costly.

His therapeutic approach saved each patient so treated and his or her insurer as much as $100,000 per year in medical costs (Beutler, 1996). He was a pioneer and an intellectual force studying the epidemiology, genetic basis, pathogenesis, diagnosis, and treatment of Gaucher and, arguably, the leading authority on the disease (Beutler, 2006c; Beutler and Grabowski, 2000). He published over 100 scientific papers on some aspect of the disorder.

When Beutler was at City of Hope he amassed a large array of references that he used in the preparation of papers and book chapters. He applied a manual card-sorting device for reclaiming references he needed, and had a programmer develop a technique that he could apply using a PDP-11/40 computer to permit him to recover references by keyword or author. Indeed, he
was so dependent on this database that he bought the PDP-11/40 to take with him when he moved from City of Hope to Scripps. The programmer who managed the database left and the code was in assembly language, so Beutler decided to develop more practical software. Beutler’s son, Earl, was head of the software division of a firm in La Jolla, and Beutler tried to get him to write the program and commercialize it. Earl had more important tasks confronting him so Beutler, after learning some basics about programming from Earl, did it himself. This was the prototype of what became known as “Reference Manager” (Beutler, 1986). This pioneering effort was a reflection of Beutler’s versatility and ingenuity and left a continuing legacy to those of us who construct scientific bibliographies.

Beutler and his colleague Dennis Carson recognizing the molecular basis of B-lymphocyte destruction in congenital adenosine deaminase deficiency realized that a designed drug inhibiting that enzyme might be of therapeutic value in lymphocyte malignancies. Carson synthesized 2-chlorodeoxyadenosine (2-CDA), a purine analog and potent inhibitor of adenosine deaminase, which was found to be cytolytic for a variety of malignant lymphocytes (Carson et al., 1984). Through a process of trial and error it became apparent that the neoplastic cells in an uncommon human lymphocytic leukemia, called hairy cell leukemia, were especially sensitive to the drug. Because the tumor was infrequent (an orphan disease), the pharmaceutical industry was not interested in developing the drug. Beutler’s group synthesized, purified, and packaged the drug and provided it to the Scripps pharmacy for human use. They
also monitored blood levels of the drug with a radioimmunoassay they developed. In a clinical study published in the *New England Journal of Medicine* they demonstrated that a single seven-day course of the drug resulted in a high fraction of patients entering a prolonged remission of the disease (Piro et al., 1990). This result was remarkable because the disease had been notoriously resistant to other forms of chemotherapy. The fact that Beutler straddled basic and clinical science, was a practicing hematologist and a biochemist, and was undaunted by the pharmaceutical industry’s disinterest, resulted in a spectacularly successful single drug regimen that resulted in a very long-term remission or cure for over 90 percent of patients with this hematological malignancy. This one achievement (in collaboration with Carson) would have represented the acme of most physicians’ careers.

Beutler was characterized by fiercely independent thought and was a proponent of evidence-based medicine long before that rubric became popular. He had earlier shown the equivalent beneficial effects of recombinant enzyme treatment for Gaucher disease when administered at a much lower dose than the company’s recommendation, saving the patient and the insurer considerable cost (see above.) He showed the waste of banked platelet transfusion products as well, often given to patients with acute leukemia whose platelet counts fell to less than 20×10⁹/L. He argued that there were no data to support such a practice and showed that using this arbitrary threshold to administer platelets was wasteful and contributed to platelet refractoriness from
Figure 2. Leading hematologists at dinner at the American Society of Hematology meeting, San Francisco, CA, December 1983.
Seated, left to right: John W. Harris, Helen M. Ranney, Samuel I. Rapaport, Ralph O. Wallerstein, Maxwell M. Wintrobe.
Standing, left to right: C. Lockard Conley, Ernest Beutler, Ernst R. Jaffé, George Brecher, Eugene P. Cronkite, Joseph F. Ross. The hematologists in this photograph each served as President of the American Society of Hematology.
allo-immunization (Beutler, 1993). He has been shown to be correct and the practice of using that threshold for automatic “prophylactic” platelet transfusion has been abandoned.

At Scripps he revisited his longstanding interest in iron metabolism and its disorders, using advanced molecular and genetic tools, decades after his first paper on the subject of iron deficiency in 1954 (Beutler et al., 1954c). He made several contributions to our understanding of the pathogenesis and treatment of iron deficiency described in over 100 papers on these topics, and at Scripps he became involved in the study of the pathogenesis and genetic basis of hereditary hemochromatosis. He lost the race to clone the gene, \textit{HFE}, for the disease. He did go on to show that although the mutation frequency in the population was high, the appearance of the clinical disease was much less frequent than was anticipated (low penetrance) (Beutler, 2003). This finding required a change in the interpretation of screening programs and the management of those who did not express biochemical evidence of disease, lest they be treated unnecessarily (Beutler, 2006b, 2007).

Beutler continued his studies of iron deficiency. The proteins involved in iron metabolism were found to be numerous and complex. The protein hepcidin (gene \textit{HAMP}) was found to be a centerpiece of the control of body iron levels. Beutler’s son Bruce, a geneticist also directing a department at Scripps Research Institute at that time, had found a mutant mouse with iron deficiency as a result of a mutation in a gene referred to as \textit{Mask}. Bruce not surprisingly enlisted his father, an authority on the metabolism of iron, to collaborate with him and
they discovered the role of a new protein, TMPRSS6, in the control of iron uptake, providing another element in the regulatory control of body iron. TMPRSS6 is an essential component of a pathway that detects iron deficiency and blocks HAMP transcription and the production of hepcidin, permitting enhanced dietary iron absorption (Du et al., 2008).

Beutler, having shown that 2-chlorodeoxyadenosine (cladribine) was immunosuppressive as well as lymphocytolytic (see above), initiated studies showing its
efficacy in patients with progressive multiple sclerosis (Beutler et al., 1996; Romine et al., 1999). This effort was of particular significance to him because his sister, Ruth, had the disease.

**OTHER ACADEMIC ACTIVITIES**

Beutler served on numerous editorial boards in the field of hematology, nutrition, and genetics. In 1972 he was a founding editor of *Hematology*, a principal textbook in the field, now in its eighth edition as *Williams Hematology*. He edited and contributed several chapters to each edition over a 38-year period. He was the founding editor of *Blood Cells, Molecules, and Diseases* in 1995, one of the first electronic journals dedicated to rapid publication, originally hosted on the Scripps server until he transferred ownership to Academic Press.

He was a former president of the American Society of Hematology and of the Western Association of Physicians. He was a member of the National Academy of Sciences (elected in 1976), Institute of Medicine, American Academy of Arts and Sciences, American Society of Clinical Investigation, and the Association of American Physicians. He received the Gairdner Foundation Award and an honorary doctorate from Tel Aviv University. He was the first recipient of the Wallace Coulter Award for Life-Time Achievement in Hematology. The American Society of Hematology established the annual Ernest Beutler Lecture and Prize in his memory and honor. Beutler, in the last weeks of his life, endowed this prize and lecture as a measure of his respect for the society as a major force in
CONCLUDING REMARKS

No doubt I have omitted important discoveries, scientific papers, monographs, books, book chapters, professional activities, and other legacies of Ernest Beutler. It is unlikely in

supporting hematology research and education. In addition, he served as the director of clinical hematology programs at the City of Hope Medical Center and subsequently the Scripps Clinic for most of his career.

Figure 4. Ernest Beutler receiving the E. Donnall Thomas Prize at the American Society of Hematology meeting December, 2003 following his delivery of the Thomas lecture. Left to right: E. Donnall Thomas (Recipient of the Nobel Prize in Physiology or Medicine, 1990), Beutler, Ronald Hoffman, President of the American Society of Hematology, 2003.
our increasingly specialized world that we will see in the future a medical scientist whose intellect, curiosity, insight, and industry will be displayed over such a broad landscape of scientific and medical problems, ranging from the identification that nonanemic women with iron deficiency are symptomatic and require therapy, the appropriate application of platelet transfusion therapy, the development of a curative drug for leukemia, and the cloning of the gene used to develop the product that provided optimal therapy for a lysosomal disorder, Gaucher disease. I, as so many others among his contemporaries, learned much from having the extraordinarily good fortune to be in his universe as a student, colleague, and friend. Ernest Beutler was the preeminent research hematologist of his day.
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