



Elizabeth Barrett-Connor: Instrumental Contributor to the Understanding of Midlife Well- being and Health in Both Women and Men

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When asked what her motto or philosophy of life was in an interview for her local newspaper, *La Jolla Light*, Elizabeth Barrett-Connor's response was that she did not have any one particular philosophy so much as an attitude: "My defining principle is that I am a pathological optimist." Boundlessly curious, fearless, challenging, inspiring, and great fun to be with are some of the words her colleagues and mentees might use to describe her. Elizabeth Barrett-Connor, MD, FACP, FAHA, is internationally acclaimed with a stellar record of research accomplishments (over one thousand original research publications), is on all the highly cited researcher lists, has been a principal investigator on numerous major population studies and multicenter clinical trials, and has received extensive grants and awards. Her immense impact is not just in research but is also reflected through her teaching, encouragement, and mentorship of generations of physicians and scientists.

Early Career

Elizabeth Barrett-Connor was born in Evanston, Illinois, to Florence (Hershey) and Willard Barrett. Her father was a Cornell University PhD chemist who worked for ammunition companies during the Second World War years, so the family moved quite a bit, ending up in the little town of Lee, Massachusetts.



Elizabeth Barrett-Connor

on the lawn listening to the Boston Pops at Tanglewood and seeing Leonard Bernstein on orchestra. "Glory days," she says. Elizabeth was an only child who loved horses, the outdoors, and visiting grandparents. Her Grandmother Barrett was postmistress in a small western New York village. Elizabeth learned to read from the postcards with her grandmother prior to delivery. Her Grandmother Hershey was from Mount Joy, Pennsylvania, and helped run a dairy. Mrs. Barrett, who thought that being lead cheerleader was not sufficient, pulled Elizabeth out of public high school and enrolled her at Northfield Preparatory School. Following Northfield, Elizabeth went on to

Mount Holyoke College where she was a Phi Beta Kappa member and a class leader. One day while headed to take a train to sit exams for nursing school, she encountered a classmate who cautioned, "You should not do that. . . . You cannot take orders from anyone!" In that one brief observation, her life charted a new path.

She graduated from Mount Holyoke College with a bachelor of science degree in zoology. Continuing her studies, Elizabeth earned her doctor of medicine degree from Cornell University Medical College in 1960. Her early interest in research was already evident in her first publication in 1959 while still a medical student, "The Diarrhea of Travelers. II. Bacteriologic Studies of U.S. Students in Mexico" (1).

After completing her internal medicine internship and residency at the University of Texas Southwestern Medical School in 1963, she studied at the London School of Hygiene & Tropical Medicine where she received a National Institutes of Health (NIH) postdoctoral fellowship. She received her diploma in Clinical Medicine of the Tropics in 1965; that same year she was married in The Church of Scotland (near Harrods in London) to James (Jim) Connor, MD, a specialist in pediatric infectious diseases. (Later, in 1985, Elizabeth also received an honorary Doctor of Science from Mount Holyoke College.)

She was appointed to the faculty of the University of Miami School of

University of Cambridge, Cambridge, U.K.

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Eight-year-old Elizabeth with her mother, Florence H. Barrett

Medicine in 1965 and established distinction as an infectious disease epidemiologist. Publications on a wealth of topics including shigellosis, infectious diarrheas, amebiasis, gonorrhea, tuberculosis, and malaria were an early indicator of her wide interests and abilities.

In 1970, her husband was recruited to be chief of pediatric infectious disease in the newly established University of California, San Diego (UCSD) School of Medicine, and Elizabeth Barrett-Connor was appointed assistant professor of Community Medicine at UCSD. This required going in a completely new research direction.

The Rancho Bernardo Study

At UCSD, Dr. Barrett-Connor took on the new challenge of starting the Rancho Bernardo Study (2). This was one of the 12 centers established for the groundbreaking Lipid Research Clinics (LRC) studies to lead research into the population prevalence of hyperlipidemia and to recruit participants to a clinical trial of cholesterol lowering for heart disease prevention. Her role as leader of the LRC Prevalence Study enabled her to establish a cohort of community-dwelling men and women aged 30 years and older in 1972. From its inception, Elizabeth Barrett-Connor had the foresight to expand the study beyond lipids by collecting additional information on a range of cardiovascular disease risk factors and lifestyle as well as setting up a biological sample bank. Because of her

foresight and creativity, she established the Rancho Bernardo Study with the capacity to address a wide range of questions relating to health of the population and the flexibility to develop over time. The Rancho Bernardo Study is still going strong over four decades later. Many of the early prospective studies oriented around heart disease were predominantly focused on men. Through the Rancho Bernardo Study, Dr. Barrett-Connor played a key role in highlighting the need for additional research in women, as well as men, and her work has been instrumental in contributing toward understanding and improving well-being and health in midlife through better prevention and care in both women and men.

The prospective Rancho Bernardo Study has provided a wealth of data on sex differences in many diseases, most notably cardiovascular disease, osteoporosis, and diabetes, and the central role played by midlife (menopausal) changes in women. So much of what she pioneered is now so well established in mainstream epidemiologic research that it may be difficult to realize how groundbreaking her approach was at the time. She was one of the earliest researchers to illustrate the scientific value of examining in a population a broad range of physiologic measures and biomarkers such as glucose metabolism, sex hormones, thyroid function, and cytokines; detailed lifestyle factors including diet and physical activity; psychosocial factors such as depression, the role of social status, education, and stress; and new phenotypes including clinical measurements of eyes and bones, as well as functional health (3–13). She recalls that one of the comments at the time was “Why would you want to study normal people?” However, it was this foresight that led to the broad scope of the Rancho Bernardo Study beyond cardiovascular disease to aging, chronic disease, cancer, dementia, osteoporosis, and, of course, diabetes, and her approach has had a lasting impact on how population studies are now designed. Dr. Barrett-Connor was one of the earliest to demonstrate the huge scientific value of stored blood samples collected at baseline to test new hypotheses arising, as new technologies became available, in cohorts followed longitudinally over decades,

transforming the ability of large population studies to elucidate biological mechanisms. This approach, for example, informed the design of the European Prospective Investigation into Cancer and Nutrition (EPIC), a half-million-participant, 10-country international collaboration now into its third decade (14), and the UK Biobank Study of half a million participants (15): her methodological influence has been enormous. Today, large population-based biological banks are now commonplace.

The Rancho Bernardo Study’s scientific contributions under Elizabeth Barrett-Connor’s leadership continue and are evidenced by the recurrent funding long after the completion of the original LRC research funding. It has been continuously funded by competitive NIH R01 grants, including four MERIT (Method To Extend Research in Time) awards from the NIH National Institute on Aging, an extraordinary achievement.

What has exemplified her approach has been her intellectual curiosity in understanding the underlying biological and behavioral basis of diseases through better characterization of these in population studies. She was also insistent on studying outcomes relevant to her population, not just disease-focused outcomes but functional and psychosocial well-being (now taken for granted but much less so at the time), was always willing to challenge conventional wisdom, and was able to provide original new perspectives on observations long taken for granted.

From the beginning, she was interested in why men had more heart disease than women and why diabetes appeared to eliminate the female advantage. The observation that women’s risk changed at midlife led to a menopause focus, partly hormonal and partly on other psychosocial, reproductive, and behavioral characteristics that might differ by sex. Based on the Rancho Bernardo Study, she was among the first to show that women have more clustered risk factors than men, that people (especially women) with diabetes have a high triglyceride/low HDL dyslipidemia, that diabetes eliminates the usual female protection against heart disease, and that the cluster of classical risk factors may explain most of this loss of protection. She was also the first to show that fasting glucose is a heart disease risk

factor, that isolated postchallenge hyperglycemia is more common and a stronger heart disease risk factor than fasting hyperglycemia, and that proinsulin is a stronger heart disease risk factor than serum insulin (3,7,16–22).

The Rancho Bernardo Study was one of the first population studies to use innovative technologies of that time to assess bone density. In osteoporosis-related Rancho Bernardo Study publications, she was among the first to show that low dietary calcium predicts future hip fractures (23), that midlife cigarette smoking predicts osteoporosis assessed as low bone mineral density (BMD) (24), that lifetime coffee intake precedes low BMD only in women who did not drink milk (25), and a U-shaped relationship exists between retinol and BMD in that low retinol (a marker for red meat consumption) and high retinol (a marker for supplements) are each associated with low BMD (26). As an example of the value of studying risk factors across different disease boundaries, she was also the first to show that diabetes, higher fasting insulin levels, and higher IGF-1 levels are each associated with better BMD at the hip and spine, but only in women (27,28).

She was the first to report that hormone replacement therapy was associated with lower risk of all-cause mortality and cardiovascular mortality in an epidemiologic study and that the latter effect was mediated by more favorable HDL levels (29–32). She was also one of the first to emphasize the prevention and compliance biases that could explain these associations (33) and played a central role in insisting on clinical trials (34). She has written about the hazards of post hoc analyses and encouraged a conservative interpretation of such trial results (35–39).

From Observational to Intervention Studies

In addition to the wealth of contributions from the Rancho Bernardo Study, Elizabeth Barrett-Connor played a key role in intervention studies building on observational data.

She was co-principal investigator (PI) until 2017 on the landmark Diabetes Prevention Program (DPP) and the Diabetes Prevention Program Outcomes Study (DPPOS) (40).

However, it is not just in the lifestyle intervention in diabetes prevention and

outcomes trials that she has had a seminal role. She has been the local, national, or international PI on multicenter clinical trials studying noncontraceptive estrogen or selective estrogen modulators on cardiovascular outcomes and bone-specific medications on osteoporotic fracture outcomes. For example, she has been a leader in clinical trials related to women's health—particularly studies of hormone replacement therapy, selective estrogen receptor modulators, and bisphosphonates, including being a national PI of the Postmenopausal Estrogen/Progestin Interventions (PEPI) study, San Diego PI of the Heart and Estrogen/progestin Replacement Study (HERS), San Diego PI of the Fracture Intervention Trial (FIT)/FIT Long-term Extension (FLEX) study and of Multiple Outcomes of Raloxifene Evaluation (MORE)/Continuing Outcomes Relevant to Evista (CORE), and international PI of the Raloxifene Use for The Heart (RUTH) trial (41–47).

Just as she was a strong voice in emphasizing the importance of studying heart disease in women as well as men, she also highlighted the importance of studying overlooked issues in men's health, such as osteoporosis. She served as the San Diego PI of the Osteoporotic Fractures in Men Study (MrOs) (41), the local PI for an NIH-funded multisite project investigating testosterone and men's health (Testosterone Trials [T Trials]) (48), and as a coinvestigator for one of its ancillary studies, the Bone Trial of the T Trials. She is a coinvestigator on two NIH-funded studies, "Association of Alcohol and Nutrition with Cognitive and Brain Structure in Aging" with PI Linda McEvoy (UCSD) and "Restorative Yoga for Therapy of the Metabolic Syndrome" (RHYTHMS) with PI Happy Araneta (UCSD). In addition, she served on the data and safety monitoring board/observational study monitoring board of the Women's Health Initiative (WHI).

However, her contributions extend far beyond research.

Although she no longer sees patients in clinical practice, she continued to see many participants in clinical trials both as examining physician and as the health educator related to retention activities and explanation of trial results. A member of seven editorial boards, she reviewed at least one manuscript per week. She served on the Preventive Medicine residency and other advisory committees at UCSD. In 2016, she

stepped down as chief of the Division of Epidemiology and distinguished professor in the Department of Family and Preventive Medicine and the Department of Medicine at the UCSD School of Medicine in La Jolla after 40 years of service.

In addition, she is a member of numerous scholarly societies and professional boards, including the Scientific Committee for the Center for Women's Health Research at the University of Colorado. She is past president of the Epidemiology Section of the American Public Health Association, the Epidemiology Council of the American Heart Association (AHA), the Society for Epidemiologic Research, and the American Epidemiological Society. She is a member of the Institute of Medicine and Master of the American College of Physicians.

Teaching and Mentorship

Elizabeth Barrett-Connor is a teacher and mentor par excellence. She established and organized the UCSD core epidemiology and biostatistics course, relinquishing responsibility for it in 2006, after 35 years. This course was designed to teach clinical research methodology and logical inference, as well as the intelligent reading and interpretation of the medical literature. She always received the highest evaluations and numerous teaching excellence awards. She continues to teach in this course and give lectures in other courses.

She has advanced not only science but the development of younger scientists from around the world. More than 50 young medical professionals have trained with her. I count myself privileged to have been one who spent four very happy years in UCSD in the 1980s. She is an inspirational and immensely generous teacher who motivates by encouragement and example. Her focus has always been less on being first/senior author than on serving as a mentor to further junior colleagues' publications and as a colleague on large multisite studies. She has introduced numerous students, postdoctoral fellows, visiting scholars, and junior faculty to the excitement and rigor of research. "She makes work such fun" extends beyond UCSD, nationally and internationally, through all her other activities.

In addition to her many other commitments, she has continually served on the faculty at an annual U.S. cardiovascular

epidemiology course. She also volunteered time for the AHA's annual 10-day international cardiovascular disease teaching seminar founded over 40 years ago by Drs. Jeremiah Stamler and Geoffrey Rose. This seminar, which provides training without cost for the participants (critical in the case of low-income countries) has trained more than 1,800 physicians and scientists from over 100 countries, many of whom are now leaders in the field. She is an outstanding lecturer and teacher, but her mentorship continues well beyond the formal training. All who have had the good fortune of meeting her have been immensely impressed by her willingness to review work in which she may not be directly involved. She has offered suggestions for improvement and provided career path advice to researchers, particularly women at various stages of their academic development. They know they can count on her guidance and support virtually indefinitely, and they continue to rely on her advice.

Awards and Honors

Her honors are too many to list comprehensively but include national and international research and teaching and awards from societies and organizations such as the American Heart Association, the American Diabetes Association, the Endocrine Society, the American College of Physicians, the NIH, and the International Academy of Cardiology (see APPENDIX). In 2018, she received the Fred Conrad Koch Lifetime Achievement Award for her contributions in endocrine physiology and the role of hormones in disease pathogenesis in cardiovascular disease, diabetes, osteoporosis, and breast cancer. The laudation by Nanette Santoro, MD, PhD, at the Koch Award celebration said, "Her ability to question earlier observational studies reflects a career-long dedication to confirming observations in randomized trials. Her scientific discipline and ability to identify methodological flaws make her an ultimate 'seeker of truth.' She has helped make women more visible in the endocrinology field, not by example of her own shining star, but by her constant recognition of light coming from others."

Other Interests

Elizabeth Barrett-Connor's formidable accomplishments would be intimidating to any young researcher, but her warmth

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Attending the Fred Conrad Koch Lifetime Achievement Award ceremony. Standing, left to right: Eva S. Liu, MD; Susan Mendel, MD, MPH; Gail K. Adler, MD, PhD; Ellen Wells Seely, MD; and Ghada El-Hajj Fuleihan, MD, MPH. Seated, left to right: Elizabeth Barrett-Connor, MD, FACP, FAHA, and Carolyn B. Becker, MD

what strike you when meeting her. It would be easy to imagine that she has only managed her achievements by focusing on work, but she is no narrow academic. As a prolific reader, she has passed on many of the books she has read between teaching sessions during seminars, offering perceptive comments on what the recipient might enjoy reading. She said that one of the joys of moving to La Jolla was the sea, which she has always loved. She could walk from their house to the sea for her regular swim. She is an intrepid swimmer and trained lifeguard. At the cardiovascular seminars held in Lake Tahoe, she was always the first to plunge into the lake's glacial waters as well as lead the white water rafting down the Truckee River. While attending international teaching seminars, she enthusiastically joined in all the expeditions, whether learning to scuba dive in Seychelles or navigating the precipitous Levada trails of Madeira.



The family at the 1993 graduation of son Steven Connor at the University of California, Santa Barbara. Left to right: Jonathan Connor, Elizabeth Barrett-Connor, Jim Connor, Steven Connor, and Caroline Connor

She and Jim delight in their children and grandchildren. Jonathan, Caroline, and Steven Connor live in San Diego with their families. Both Jim and Elizabeth are great cooks and hosts, providing family, colleagues, and visiting researchers with many happy memories of jolly barbecues and potlucks at their house in La Jolla.

Her research contributions in any single field would be outstanding, but what is absolutely remarkable is her acknowledged and recognized impact over a whole span of population health: diabetes, osteoporosis, cardiovascular disease, endocrinology, women's health, and aging. And for all of us who love and admire her, we can only express appreciation for her enthusiasm and generosity in training, inspiring, and supporting generations of researchers. Elizabeth Barrett-Connor's ready wit may deem herself a "pathological optimist," but that optimism has resulted in a lifetime of many exceptional achievements.

Appendix

Awards include the Women in Epidemiology, Epidemiology and Prevention Mentoring Award (EPI/NPAM, 2013); Distinguished Fellowship Award, International Academy of Cardiology (2013); Endocrine Society Mentoring Award (2012); AHA Population Research Prize (2011); AHA Distinguished Scientist Award (2009); National Osteoporosis Foundation Living Legacy Award (2009); Endocrine Society Clinical Investigator Award (2003); Cornell University Medical College Alumni Association Award of Distinction (2003); American Society for Preventive Cardiology Stokes Award (2003); London School of Hygiene & Tropical Medicine Heath Clark Lectureship (1999); NIH Award for Outstanding Work in Gender Differences in Osteoporosis (1999); American Epidemiological Society Harry S. Feldman Lecture (1998); Society for Epidemiologic Research John C. Cassel Memorial Lecture (1997); NIH Florence Mahoney Lecture on Aging (1996); AHA Ancel Keys Memorial Lecture (1995); American College of Physicians James D. Bruce Memorial Award (1994); American Public Health Association Wade Hampton Frost Lecture (1993); American Diabetes Association Kelly West Memorial Lecture/Award (1987); and the American College of Preventive Medicine Katharine Boucot Sturgis Lecture (1986).

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