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SYMPOSIUM: BONE QUALITY: FROM BENCH TO BEDSIDE

Biographical Sketch

Fuller Albright, MD 1900–1969

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Abstract This biographical sketch on Fuller Albright corresponds to the historic text, The Classic: The Metabolic Effects of Steroid Hormones in Osteoporosis, available at DOI 10.1007/s11999-011-1832-z.

Fuller Albright, MD (1900–1969), was neither a surgeon nor an orthopaedic specialist, but the endocrinologist's insights into gender differences and bone health formed the foundation of our understanding of the relationship between menopause and osteoporosis.

Albright was born in Buffalo, NY, the son of a wealthy industrialist. He matriculated to Harvard College at 17, was graduated in just three years (with a brief interruption for stateside military service during World War I), and entered that institution's medical school in 1920. He intended to become an orthopaedic surgeon, but decided that he lacked the requisite manual dexterity [35]. During his years in medical school, the profession of medicine was changing because of tremendous advances in biochemistry, chief among them the synthesis of insulin as therapy for diabetic patients [20]. Albright's interests turned to endocrinology, particularly the metabolism of calcium, becoming a primary area of research for the rest of his working life. He served his residency at Massachusetts General Hospital, and then a research year with Joseph Aub, an expert in lead poisoning who further nurtured his interests in endocrinology. After a year of residency at Johns Hopkins and another year of study with the Austrian pathologist Jacob Erdheim, he returned to Massachusetts General and Harvard in 1929 to practice, teach, and investigate [35]. There he developed an endocrinology research division that became the Stone Clinic in 1936.

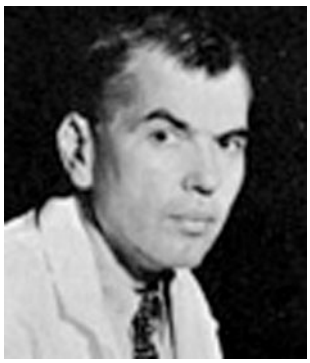

Fig. 1 Fuller Albright, MD.

Albright accomplished a great deal in a relatively short amount of time, and his name quickly became associated with a number of metabolic disorders he was among the first to describe. Most notably, in 1937, he published a description of a congenital disorder that begins in childhood or early adolescence and combines polyostotic fibrous bone dysplasia (most commonly affecting the long bones), light brown skin pigmentation, and endocrine disorders such as precocious puberty in girls. This became known as Albright Syndrome [12] (or McCune-Albright Syndrome, after Donovan McCune, who also described it independently [36]). Much of his research involved hyperparathyroidism, or overactivity of the parathyroid glands that results in excess production of parathyroid hormone, which regulates the body's calcium and phosphate levels [4–10, 13, 15, 16, 18, 25, 26, 32]. He identified a method to measure gonadotropins in urine, which enabled the

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diagnosis of testicular disorders and amenorrhoea [22, 29, 37], and contributed greatly to our understanding of the pathogenesis of Cushing's syndrome [14, 21, 28, 33]. His research in Cushing's led him to participate in early attempts at steroid therapy, and he was among the first to describe the negative effects of these drugs [14, 28, 40, 41]. He successfully advocated medical curettage for bleeding from endometrial hyperplasia, reducing the need for surgical dilation and curettage in cases in which cancer was suspected [31]. In 1948 he and colleague Edward C. Reifenstein published their classic book, "The Parathyroid Glands and Metabolic Bone Disease".

The culmination of decades of research and speculation, one of Albright's greatest discoveries was the makeup of human and avian bones. Osteoporosis has been identified in 4,000-year-old Egyptian mummies and depicted in old women in Renaissance paintings [38]. Elderly women are often described in literature as stooped or humped; for example, when the reader first meets old Miss Havisham in Charles Dicken's "Great Expectations" (1861), we are told "Her chest had dropped, so that she stooped," her physical appearance presumably mirroring her decrepit soul [24]. The Scottish surgeon John Hunter (1728–1793) observed bone remodeling in the 1770s, but further explanation eluded him. The French surgeon and pathologist Jean Georges Chretien Frederic Martin Lobstein (1777–1835) gave the name "osteoporosis" to describe the porous bones he observed in autopsies [38]. However, by the mid-20th century, the only known causes of osteoporosis were atrophy and age; in other cases, the disease was termed idiopathic.

Albright was aware of research in the mid-1930s linking ovarian function and the metabolism of calcium in pigeons. Male pigeons had been shown to be osteoporotic compared to ovulating females [34]. In 1938, a pair of researchers injected male pigeons with estrogen and found it led to improved bone formation [39]. Albright observed a large number of his patients with idiopathic osteoporosis were postmenopausal women, and he speculated that estrogen would stimulate osteoblasts to form improved bone matrix. Albright put three of them on estrogen therapy (1.66 mg of beta-estradiol benzoate every other day). He noted that while the administration of estrogen had immediate positive effects on phosphorous and calcium balance, "the maximum effect was not reached until after twenty days. … the effect then continued as long as estrogen was administered (98 days), and following cessation of treatment there was little change for about 15 days, then a slow reversal to pre-medication findings" [11]. A second course of treatment then restored the correct calcium/phosphate balance. Albright was extremely cautious in reporting even positive results; he ended his report by writing that "whether the effect of estrogen on the calcium balance in postmenopausal osteoporosis is sufficient to make its administration of practical clinical value, it is as yet too soon to say" [11]. The title of the article gave the condition a new name: "Menopausal Osteoporosis". Albright's continued work through the 1940s established the practical clinical value of estrogen; controversy over the pros and cons of the therapy continue to this day.

One of the most persistent controversies regarding estrogen therapy is its link to endometrial cancer [23]. Albright was aware of this and was among the earliest adopters of the "Pap smear" examination in 1941 [27]. As early as 1938, Albright had proposed the treatment of endometrial hyperplasia with injections of progesterone, a steroid hormone that among its effects suppresses ovulation [1]. Albright had, unintentionally, outlined how hormonal contraceptives could be developed. He did not pursue this in his research or teaching, because his focus on was on prevention of endometrial cancer and subsequent oophorectomy, and because Massachusetts law forbade not only contraceptives, but the dissemination of any information about them [27]. Albright was keenly aware of what would follow; his prediction of eventual "birth control by hormone therapy" in 1945 has come to be known as "Albright's prophecy" [17].

Despite his successes, Albright was a notably humble and humorous individual. He described being a clinical investigator as "trying to ride two horses – attempting to be an investigator and a clinician at the same time." Fortunately, he wrote, his patients always reminded him not only of his purpose but helped provide the answers:

> In the first place, the ultimate goal of most investigation is to find something of benefit to the human race; where, other than by the bedside of sick patients, could one find so many suggestions of things to be investigated? Secondly, in many instances, nature has arranged an experiment in a sick individual and partly completed it; all that is needed are the eyes of the clinician to make certain observations, and the background of the investigator to plan other observations and interpret them. … an intelligent patient, private or otherwise, to whom you have taken the trouble to explain the nature of the investigation, makes the best laboratory animal [2].

He concluded one of his papers with these words: "(1.) I have told you more than I know about osteoporosis. (2.) What I have told you is subject to change without notice. (3.) I hope I raised more questions than I have given answers. (4.) In any case, as usual, a lot more work is necessary" [3]. This breezy approach to explaining his results belied the incredibly meticulous work in collecting them. Conducting a study on metabolic balance meant buying, preparing, and preserving all food for research

subjects; weighing all food served; collecting stool samples and urine; rinsing bedpans; and monitoring subject activities to keep them as constant as possible [40]. Elaborate "circuit board" diagrams were drawn to establish working hypotheses and a complicated system created to chart data visually [3]. As one colleague wrote in remembrance, "An intellectual athlete, he loved a problem in the way that a good athlete loves to ski" [19]. Strangely, given his diligence in collecting data, he disregarded statistical methods, preferring to concentrate intensely on small numbers of patients rather than large populations. "I'm sure (statistics) are important, but if you have to use them, I don't believe it," he told a contemporary [19].

His good humor extended to the great tragedy of his life. In 1937, the 36-year-old Albright was diagnosed with Parkinson's disease, the symptoms of which grew gradually but relentlessly worse over the next decade and a half. At age 46, he wrote "For the past ten years, I have had the interesting experience of observing the development of Parkinson's syndrome on myself. As a matter of fact, this condition does not come under my special medical interests or I would have solved it long ago." He mentioned another ancillary benefit to the disease: "One avoids all kinds of deadly committee meetings. …" By the early 1950s his wife, colleagues, and students found him in increasing need of day-to-day assistance, tying his shoelaces, helping him through the cafeteria, writing his notes, holding his stethoscope, and driving him to and from work [19]. In 1956, Albright, against the advice of several physicians, decided to undergo a pallidotomy, a then-newly proposed treatment for Parkinson's in which a section of the globus pallidus is destroyed in an attempt to reduce movement symptoms. He suffered a brain hemorrhage as a result of the procedure and spent the remaining 13 years of his life in akinetic mutism at Massachusetts General [35]. In recognition of both his accomplishments and the fact that he began making them at such an early stage in his career, the American Society for Bone and Mineral Research established the Fuller Albright Award, which is given to a researcher age 40 or younger who achieves a significant scientific milestone [30].

His medical career thus ended prematurely, but his accomplishments exceeded a normal lifetime's work. Any one of his discoveries—in osteoporosis, Cushing's disease, hyperparathyroidism—would be enough to secure a place in medical history. Above all, he would be remembered well enough by his colleagues for his good humor and his generosity in sharing information and credit for his work. Albright once listed for his colleagues a collection of "Do's" and "Do Nots" that led to the "door of success" in clinical research. (For example, he recommended that researchers always ask themselves what they are measuring, but at the same time avoid being fooled by data; always develop a theory but never be a slave to it; and—only partially tongue in cheek—"do not show too much administrative ability" or the researcher will "wake up some fine morning in an executive job.") Even if one followed his advice, he said, "You will still need the key to open the door. The key stands for the personal equation. 'But personality does not count in pure science,' you say. That may be true, but Clinical Investigation is not a pure science" [2].

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