Fuller Albright: The Consummate Clinical Investigator

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The authors have been involved in the study of mineral metabolism for a good part of our academic careers. As such, we have admired, studied, and benefited from the scientific work and writings of Fuller Albright, whose productive career at Harvard Medical School and the Massachusetts General Hospital spanned almost 30 yr from the late 1920s until 1956. The senior author, Charles Kleeman, was a house officer at Boston City Hospital in 1948 when he first read Fuller Albright’s remarkable book Parathyroid Glands and Metabolic Bone Disease (1). This landmark publication summarized Albright’s many contributions to mineral metabolism during the previous two decades. Our goal in this historical review is: 1) to describe Albright, the man and his life; 2) review some of his major research accomplishments; and 3) conclude by citing an appreciation of Albright by several of his coworkers and trainees.

Fuller Albright was born in Buffalo, New York, on January 12, 1900. His father was a wealthy industrialist and philanthropist. The major art museum in Buffalo is known today as the Albright-Knox Art Gallery. Albright attended the Nichols School in Buffalo, which was founded by his father. He not only excelled academically, but also was captain of the football team. During his childhood, the Albright family made frequent visits to Wilmurt Lake in the Adirondacks, where he became an avid fly fisherman and developed woodsman’s skills. During his academic years in Boston, Albright would spend summer vacations at Wilmurt Lake with his family. It was at Wilmurt Lake where he directed that his ashes be scattered after his death.

Fuller Albright attended Harvard College, but after only 18 mo, he falsified his age and enlisted in the Army after America’s entry into World War I. It was also the time of the great influenza pandemic, which has been postulated to be a cause of Parkinson’s disease many years after recovery from influenza. Albright was to develop Parkinson’s disease in his mid-30s, and it was to progress relentlessly during the next two decades of his life.

In 1921, Albright entered Harvard Medical School, where he excelled and was elected to Alpha Omega Alpha. On graduation, he did an internship and residency in Medicine at Massachusetts General Hospital. There he met Read Ellsworth, who became a close friend and collaborator. Both initially were mentored by Dr. Joseph Aub, a clinical scientist in endocrinology and metabolism. Albright and Ellsworth continued their research collaboration in mineral metabolism until the latter’s premature death from tuberculosis in 1937.

Perhaps the most critical year in Albright’s training was that of 1928–1929, when he went to Vienna to study with Dr. Jacob Erdheim, a brilliant pathologist who in 1906 had established the relationship between the parathyroid glands and calcium metabolism by showing that calcium is not deposited into growing teeth in the absence of parathyroid glands. Also, it was Erdheim who had first described compensatory hyperplasia of the parathyroid gland associated with osteomalacia (2). Albright often would later say of Erdheim that “quite simply he knew more about human disease than any other living man” and referred to him as “the greatest of living pathologists.”

Albright returned to Massachusetts General Hospital in 1929 (Figure 1A). There he would begin his long, productive career in clinical research, much of which emanated from the then recently established Ward 4, which was a 10-bed research unit where patients and healthy subjects could be intensively studied. On Ward 4, special diets could be prepared, biochemical measurements could be performed, and meticulous collections of urinary and fecal output could be obtained. The latter, when combined with measurement of dietary intake, constituted the balance study that became a major investigative tool for Albright.

Albright married Claire Birge in 1932, and they had two sons. She became a major source of support for him as his Parkinson’s disease progressed. By the early 1940s, Albright could no longer write, and by the mid-1940s his speech had become difficult to understand. In an article written in 1946 for the twenty-fifth anniversary of his medical school class enrollment, Albright wrote, “I have had the interesting experience of observing the course of Parkinson’s syndrome on myself… It disturbs every movement and gives a certain rigidity that makes small talk look strained. The condition does have its compensations: one is not taken away from interesting work to be sent to Burma, one avoids all forms of deadly committee meetings, etc.” (3).

The patients for Albright’s studies came from his three weekly clinics: the Ovarian Dysfunction Clinic on Tuesdays, the Stone Clinic on Wednesdays (also known as the Quarry), and the general Endocrine Clinic on Saturdays (4). Even when not involved in a study, every patient would return to the respective clinic at least once per year. If a patient failed to return, a visiting nurse would be sent to find the patient. In
1939, Anne Forbes became his physician administrative chief and collaborator. She assumed much of the administrative and organizational burden for his studies. In 1942, Albright became an Associate Professor of Medicine at Harvard, but not wanting any administrative burden, he refused to become a full professor.

In the 1950s, the medical student taking an elective with Albright would be given the family’s second car with the assigned task of transporting Albright to the hospital and looking after him at work. These students included such future well-known investigators as Howard Rasmussen, James Wynngaard, Steven Krane, Kurt Isselbacher, and Stan Franklin. By the early 1950s, Anne Forbes has said that Albright was convinced that the Parkinson’s disease was affecting his intellect (5). In 1952, a noted New York neurosurgeon, Dr. Irving Cooper, had reported that Parkinson’s patients could be improved by a surgical procedure, chemopallidectomy, in which small amounts of alcohol were injected into the areas of the brain responsible for the tremor and rigidity. Despite expert advice to the contrary from his Harvard colleagues and even from Dr. Cooper, Albright was determined to undergo the procedure because of his inability to speak comprehensively and a severely impaired capacity to dress, eat, and write (Figure 1B). The surgery was performed in June 1956. After the intervention on the right side, a marked improvement in symptoms was observed. However, the operation on the left side was followed by a major cerebral hemorrhage, from which Albright would never recover. For the next 13 yr, he lived in a vegetative state.

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Albright, the Clinical Investigator Par Excellence
Mineral Metabolism

Albright’s work on serum calcium and phosphorus regulation, primary hyperparathyroidism, and the renal excretion of calcium and phosphorus became the foundation of our understanding of mineral metabolism. His description and study of vitamin D resistant rickets became the basis for the study of renal phosphate transport. Starting in the late 1920s and continuing through the mid 1930s, Albright’s primary focus was studying how differences in dietary calcium and phosphate affected calcium and phosphate balance in healthy subjects and in patients with primary hyperparathyroidism and with hypoparathyroidism. Healthy subjects and patients with hypoparathyroidism were studied with the newly available parathyroid extract (PTE). Because the balance studies were remarkably consistent, only a small number of subjects needed to be studied to provide the results, which remain true today. Based on the results shown in Table 1, Albright was the first to provide a comprehensive framework for understanding the regulation of calcium and phosphate in normal subjects and in patients with parathyroid disorders.

The report of the seventeen patients operated on for primary hyperparathyroidism published by Albright in 1934 was the largest series until then (6). The number of patients in that series diagnosed with primary hyperparathyroidism had been greatly expanded when Albright had the insight to measure serum calcium values in patients with kidney stones. At diagnosis, primary hyperparathyroidism was a much more severe disease than now. The average preoperative serum calcium value was 13.9 mg/dl and the average weight of the removed parathyroid adenoma was >11 g. Parathyroidectomy was an entirely new operation for surgeons and required intensive training with autopsy material (7). Two remarkable findings characterized the first 17 parathyroidectomies. Two patients had ectopic locations of their parathyroid adenoma, one of whom was the famous Captain Martell, who required seven operations before the ectopic gland was discovered. Cases 15 through 17 had parathyroid hyperplasia and not an adenoma as the cause of the hyperparathyroidism (6).

In a discussion of a case of renal osteitis fibrosa cystica in 1937, Albright suggested that the reason for parathyroid hyperplasia was the phosphate retention in renal failure (8). He added that in the absence of parathyroid hyperplasia, there would be greater phosphate retention and a further lowering of the blood calcium. Also in 1937, Albright described a patient with rickets that was resistant to treatment with vitamin D (9). This patient was intensively studied and clearly differentiated from patients with rickets from vitamin D deficiency. The name given to the disorder by Albright, vitamin D resistant rickets, was in use for many years until it was renamed X-linked hypophosphatemic rickets. This disorder also became the basis for the study of abnormal renal phosphate transport. Finally, in 1937, Albright reported five cases of another unusual bone disorder, polyostotic fibrous dysplasia, which was associated with hyperpigmented lesions of the skin and endocrine dysfunction (10). Today the disorder is called the McCune-Albright syndrome.

In 1941 at a clinicopathological conference, Albright asked why a patient presenting with a destructive bone lesion in the right ilium from renal cell carcinoma should have hypercalcemia and hypophosphatemia (11). A neck exploration for presumed hyperparathyroidism was performed, but no abnormality was found. Albright questioned whether the tu-
mor might be responsible for ectopic production of parathyroid hormone. In the same year, Albright described a case of hypercalcemia in a 14 yr old boy who fractured his femur through a bone cyst in an athletic accident (12). After casting and bed rest, the patient developed severe hypercalcemia. Because of the hypercalcemia and the presence of a bone cyst, a parathyroid exploration was performed but no abnormalities were seen. Albright was the first to recognize that immobilization could cause hypercalcemia. A similar report of hypercalcemia following immobilization in Paget’s disease was published in 1944 (13).

In 1942 Albright described pseudohypoparathyroidism (14). In this disorder, the important concept of end-organ resistance to a hormone (PTH) was first shown. Albright chose the name, Seabright-Bantam, because this male fowl has feathers similar to the female despite having normal functioning testes. Other highlights of Albright’s investigation into disorders of calcium and phosphorus included his publication in 1946 of osteomalacia, rickets, and nephrocalcinosis in association with renal tubular acidosis (15). In 1948, Albright reported the occurrence of band keratopathy of the cornea in 19 patients with diverse causes of hypercalcemia (16). In 1949, Albright reported several patients with the chronic form of the milk alkali syndrome. These patients had chronic renal failure, hypercalcemia, soft tissue calcium deposits, band keratopathy, and nephrocalcinosis from the chronic ingestion of calcium-containing antacids (17). In 1953, Albright reported 35 patients with idiopathic hypercalciuria associated with kidney stones, hypophosphatemia, and normal serum calcium values (18).

Table 1. Summary of studies by Albright showing the effect of changes in dietary calcium and phosphate and administration of parathyroid extract in normal subjects and hypo- and hyperparathyroid patients

<table>
<thead>
<tr>
<th>Treatment of hypoparathyroidism with parathyroid extract (29)</th>
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<tbody>
<tr>
<td>1. Phosphate excretion increased immediately and reached a maximum within 2 h</td>
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<tr>
<td>2. The increase in serum calcium and decrease in serum phosphorus values both followed the increase in urine phosphate excretion</td>
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<tr>
<td>3. A critical serum calcium value was seen at 8.5 mg/dl at which negligible urine calcium excretion suddenly changed to an appreciable one</td>
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<tr>
<th>Administration of parathyroid extract given to normal subjects (30)</th>
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</thead>
<tbody>
<tr>
<td>1. Same results as patients with primary hyperparathyroidism</td>
</tr>
<tr>
<td>A. Hypercalcemia</td>
</tr>
<tr>
<td>B. Decrease in fecal calcium excretion</td>
</tr>
<tr>
<td>C. Increase in urine calcium excretion</td>
</tr>
<tr>
<td>D. More negative calcium balance on low calcium diet</td>
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<table>
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<tr>
<th>Treatment of primary hyperparathyroidism with high dietary phosphate (31)</th>
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<tbody>
<tr>
<td>1. Almost complete absorption of phosphate into the blood stream</td>
</tr>
<tr>
<td>2. Rapid excretion of the absorbed phosphate by the kidney</td>
</tr>
<tr>
<td>3. A rise of the previously low serum phosphorus value</td>
</tr>
<tr>
<td>4. A fall of the previously elevated serum calcium value</td>
</tr>
<tr>
<td>5. A fall of urinary calcium excretion</td>
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Albright concluded by citing two potential dangers of phosphate ingestion in primary hyperparathyroidism: 1) precipitation of calcium-phosphate deposits in body tissues called parathyroid poisoning by Albright and 2) production of phosphate stones in the kidney.

Pituitary, Adrenal and Gonadal Axis

While much of Albright’s first decade as a clinical investigator was devoted to studies of mineral metabolism and the diagnosis and treatment of primary hyperparathyroidism, studies of adrenal and gonadal disorders assumed greater importance in the 1940s. His elegant studies of the Cushing syndrome were highlighted in three papers published in 1941 (19–21). These studies were previously reviewed in detail by Schwartz (22), but will be summarized here. In the first paper, Albright showed that glucose intolerance and resistance to insulin were characteristic findings of the Cushing syndrome. In the second paper, Albright treated patients with the Cushing syndrome with testosterone, asking the question whether such treatment would counteract the catabolic effects seen in this syndrome. The testosterone treatment resulted in a strikingly positive nitrogen balance, a gain in weight and strength, thickening of the skin, and a reduction in abdominal protuberance (21). However, because
of the availability of adrenal surgery, the use of testosterone treatment never gained widespread use. Albright also performed several studies that helped elucidate the etiology of congenital adrenal hyperplasia, which was called the adrenogenital syndrome by Albright (22).

The paper in which Klinefelter’s syndrome was first described was published in 1942 (23). The story is told by Kolb (4) that the syndrome was discovered because the Draft Board in Boston sent recruits with prominent breasts to Albright’s clinic where small testes were noted and biopsied, and follicle stimulating hormone (FSH) levels were measured and found to be increased. Also in 1942, Albright further defined Turner’s syndrome by showing it was not of pituitary origin, but rather due to primary ovarian failure in which elevated FSH values were present (24).

Finally, it has been stated that Albright first described or contributed to the description of 14 major clinical syndromes (22). These syndromes are listed and characterized in Table 2.

**Albright, Through the Eyes of Coworkers and his Presidential Address**

Fuller Albright’s 1944 presidential address to the annual meeting of the American Society for Clinical Investigation, “Some of the Do’s and Do-Not’s in Clinical Investigation,” is important because in it he provides his personal road map for performing clinical and laboratory investigation (Figure 2). In his introduction, he states that the clinical investigator must avoid the danger that he or she, as the clinician, be swamped with patients and the equal danger that he or she, as an investigator, be segregated entirely from the bedside. Even though his advice to the investigator is shown as a road map leading to the Castle Of Success (Figure 2), Albright refuses to define success, except to say that it is more than academic recognition and self-satisfaction. The reader is strongly encouraged to read this remarkable address in which Albright provides the investigator with the gift of his wisdom. It is readily available in the archives of the *Journal of Clinical Investigation* (25).

To close our characterization of Albright and his work, appreciations from several physicians who worked with him will be cited. William Parson worked with Albright during the late 1930s and early 1940s and later became Chairman of Medicine at the University of Virginia. In 1995, Parson wrote of “Albright’s creative genius and his engaging personal qualities of unpretentiousness, good humor and wit” (26). He went on to say that Albright was the first to conceptualize two important concepts in Endocrinology, end-organ unresponsiveness to a hormone (pseudohypoparathyroidism) and hormone or hormone-like production by nonendocrine tissue (ectopic produc-

### Table 2. Major clinical syndromes initially described or further characterized by Fuller Albright

- **Acute Parathyroid Poisoning**—the increase in serum calcium values to levels that induce renal failure and hyperphosphatemia—first described during Albright’s early studies of the infusion of PTH, but also seen in patients with primary hyperparathyroidism and severe hypercalcemia (32)
- **Primary Hyperparathyroidism from hyperplasia of all glands**—described in 1934 (6) and later presented in greater detail (33)
- **Vitamin D Resistant Rickets** (9)—described in 1937 and now known as X-linked Hypophosphatemic Rickets
- **Polyostotic Fibrous Dysplasia with hyperpigmentation and gonadal dysfunction** (10)—described in 1937 and now known as the McCune-Albright syndrome
- **Hyperparathyroidism Secondary to Renal Disease** (8)—described in 1937 along with an explanation for the development of hyperparathyroidism
- **Post-menopausal Osteoporosis** (34)—discussion in 1941 with hypothesis that estrogen deficiency had a primary role
- **Pseudohypoparathyroidism with Albright Hereditary Osteodystrophy** (14)—described in 1942 and given the name of Seabright-Bantam syndrome for target organ unresponsiveness to hormone; also the patients had a phenotype of round faces, short stature, short fourth metacarpal bones, obesity, subcutaneous calcifications, and developmental delay
- **Klinefelter’s syndrome** (23)—described in 1942
- **Turner’s syndrome** (24)—expanded original description by showing in 1942 that disorder was due to ovarian failure and not pituitary abnormality
- **Renal Tubular Acidosis with Nephrocalcinosis and Osteomalacia** (15)—described in 1946
- **Milk-Alkali syndrome** (17)—description in 1949 of the chronic form of this disorder characterized by persistent hypercalcemia, renal insufficiency, and nephrocalcinosis
- **Pseudo-pseudohypoparathyroidism** (35)—description of a patient in 1952 with the classic phenotype of Albright Hereditary Osteodystrophy, but with a normal serum calcium concentration and without renal tubular resistance to parathyroid hormone
- **Idiopathic Hypercalciuria** (18)—described in 1953 in association with kidney stones
- **Forbes-Albright syndrome** (36)—description in 1954 of syndrome of hormone secreting pituitary or hypothalamic tumor causing galactorrhea and amenorrhea
tion). Parson continued, "Albright never had an interest in bench work. He felt that he could always get someone to make the measurements. The trick was to know what to measure and how to interpret the results… It was fun and exciting to work with a genius whose talent was to see relationships between facts universally considered to be unrelated.” During the study of the first patient with pseudohypoparathyroidism, Parson relates that Albright was intrigued by her unusual appearance and the failure of a “good” batch of parathyroid extract to work. Albright refused to move on, even though others wanted to substitute dihydrotachysterol treatment and drop the project.

Frederic Bartter worked with Albright in the 1940s and later became Chief of Clinical Endocrinology at the NIH. After Albright’s death in 1969, Bartter wrote a homage to Albright in which he said of Albright that clinical experiments of nature were the substrate for almost all of the inspired and systematic investigation that constituted his enormous contribution (27). He continued that Albright’s real delight was in formulating a theory to explain the unknown elements that remained, and Albright had no use for the “learned tradition.” Rather, Albright believed that progress could only be made by formulation of a precise theory and challenge of that theory.

Finally, Gilbert Gordan, who did a fellowship with Albright in the late 1940s and later became Professor of Medicine at the University of California at San Francisco, wrote in 1981 that “when Albright was working on a problem he virtually lived it every day, and he would discuss his ideas with anyone who was interested (28). Albright was completely self-assured and never concerned that someone less gifted would steal his ideas.” Gordan continued, “For every problem there were what Albright called ‘measuring sticks’ – either chemical or bioassay, or the weight of axillary hair, or displacement of water by acromegalic hands and feet, or measurement of height to determine the growth rate, etc. One of his ‘Do’s’ was – do measure something.”

In his presidential address in 1944, Albright stated that Oliver Wendell Holmes divides intellects into one-story, two-story, and three-story. The latter idealize, imagine, predict; their best illumination comes from above through the skylight. His co-workers and peers appreciated that Albright received illumination through the skylight. Albright also had the capacity to refute accepted dogma and to formulate a working hypothesis of clinical disorders, which he would continuously challenge. Finally, as in the recognition of hormone failure in pseudohypoparathyroidism, Albright understood that when all other possible explanations are eliminated, the remaining explanation no matter how improbable must be true.

Acknowledgments

Dr. Charles Kleeman wishes to dedicate this manuscript to the memory of the late Dr. Frank Epstein. Drs. Epstein and Kleeman were fellow trainees and assistant professors at Yale Medical School under the critical and watchful eye of their mentor, Professor John P. Peters. For more than 50 yr afterward, Drs. Epstein and Kleeman were collaborators and the closest of friends. Dr. Kleeman deeply mourns the recent loss of Dr. Epstein. The authors also wish to express their appreciation for the assistance of Kristen G. Ostheimer from the Rare Books and Special Collections section of the Francis A. Countway Library of Medicine, Boston, MA, who provided the requested historical material on Fuller Albright.

Disclosures

None.

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