Fuller Albright and clinical investigation

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Today's diabetes world is fast moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past. In this installment of *Tattersall's Tales*, Robert Tattersall provides a biography of US endocrinologist Fuller Albright, who had a keen focus on being a clinical investigator rather than an administrator. His approach yielded a great range of new ideas and clinical findings.

I always enjoyed clinical investigation but might not if I had been, for the sake of argument, one of 500 investigators of amaziglitazone in the ARAFAT trial (Amaziglitazone Really Acts Fantastically And Terrifically). The undisputed king in the golden age clinical investigation between 1930 and 1950 was the American endocrinologist Fuller Albright (1900–1969) whose profile I wrote in the recently published *Dictionary of Medical Biography* (Tattersall, 2006). He was not particularly interested in diabetes but I thought readers would be interested in his career and rules for clinical investigation.

Albright was the son of a wealthy father who made his money from coal, asphalt and cars. After his internship at Massachusetts General Hospital (MGH), he spent 1928–9 in Vienna with the skeletal pathologist Jacob Erdheim. He often talked about Erdheim, whose virtues were that he 'worked hard and was smart as hell', a description that might well have been applied to Albright himself. A further quality of both men was insatiable curiosity. Albright's work was varied and far reaching, covering the parathyroids, adrenals and gonads. At one time, there were at least a dozen eponymous diseases named after him and there could have been more; for example, Turner's and Kleinfelter's syndromes. In 1938, Henry Turner described seven young women with what is now called Turner's syndrome; however, at the time, he attributed it to pituitary disease. In 1942, Albright showed that the condition was due to primary ovarian insufficiency (Albright et al, 1942a). Albright had collected a group of men with gynaecomastia, small testes and elevated FSH and he generously gave their data to Harry Kleinfelter to write up. Thus, the condition is now known as Kleinfelter's syndrome (Kleinfelter et al, 1942).

Much of Albright's work was on calcium metabolism. This was stimulated by one patient, probably the most written-up in history: Sea Captain Charles Martell, who was the first person with hyperparathyroidism diagnosed in the US (Spence, 1984). Martell was born in 1896 and in the early 1920s noticed that he was shrinking and developing fractures after minor trauma. He also had generalised aches and pains in his skeleton. In 1923, he went into hospital where he was dosed with large amounts of cod liver oil and other substances that were thought to strengthen the bones. In 1926, he was admitted to a metabolic ward and, after innumerable balance studies, it was concluded that he had softening of the bones due to hyperactivity of the parathyroids. Between 1926 and 1931, several operations by expert thyroid surgeons failed to find a parathyroid tumour. When admitted under Albright in 1932, Martell had lost a full foot in height, was wheelchair bound and in constant pain. Yet, Martell, who spent a lot of time reading medical journals, was convinced that he did indeed have a parathyroid adenoma and insisted on a complete re-exploration of his neck. This revealed nothing. Finally, in November 1932, a mediastinotomy – his seventh operation – revealed an adenoma behind the sternum. Unfortunately, he died soon after from complications arising from kidney stones. Martell was probably the origin of Albright's dictum that 'an intelligent patient...to whom you have taken the trouble to explain the nature of the investigation, makes the best laboratory animal.' Those were the days of gross physical signs and Albright used to say that anything that could only be proved by statistics was probably wrong.

In 1934, Albright and associates described three patients with hyperparathyoidism due to diffuse hyperplasia of all four glands. In the same year, he coined the term 'nephrocalcinosis'. In 1937, he described vitamin D-resistant rickets and later established that the primary action of vitamin D is to increase intestinal calcium absorption. Additionally, he reported five cases of 'a syndrome characterised by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction with precocious puberty in females' – one of the many Albright's syndromes (Albright et al, 1937).

In 1942, Albright investigated a young woman with dense skull bones, epilepsy and hypocalcaemia that could not be corrected with parathyroid hormone. Albright postulated that 'the disturbance was not lack of hormone, but a resistance to it.' He speculated that there might be parathyroid antihormones or 'a deficiency of or interference with some hypothetical substance with parathyroid hormone reacts.' This led him to the so-called Seabright Bantam's syndrome. Sir John Seabright was an English landowner who, in 1800, discovered in his barnyard a single bantam rooster with female tail feathers. He bred from this individual and eventually produced the strain known as Seabright bantam. Albright hypothesised, incorrectly as it turned out, that the Seabright bantam was resistant to testosterone. Nevertheless, his paper introduced the concept of end-organ resistance to a hormone (Albright et al, 1942b).

Albright also established the concept of hormone production from nonendocrine tissue. At a clinicopathological conference in 1941, Albright made the revolutionary suggestion that the tumour of a 50-year-old Greek with a hypernephroma, hypercalcaemia and a single metastasis might be producing a parathyroid hormone-like substance, a concept which became established 25 years later. Another of Albright's ideas that was ahead of its time was his 1945 suggestion of 'birth control by hormone therapy'. This became known, in retrospect, as Albright's prophecy.

Now for Albright's 'do's' and 'do not's' (Albright, 1944). According to him, a clinical investigator has the job of trying to ride two horses, one representing investigation and the other clinical progress. Of course, 'such an equestrian manoeuvre is usually considered a bad policy...[but] experience has shown that it is a very fruitful pastime… the clinical half will constantly be interrupted by messages such as

that Mr Humpty Dumpty has had a great fall ...[so] the clinical investigator can never hope to publish as many papers as those doing 'animal or smoked drum experiments'.

The 'do's' included 'look at the problem from all points of view', 'measure something' and 'develop a theory'. According to his associates, he had an amazing capacity for collecting facts from other disciplines and developing hypotheses that could be tested. Nevertheless, he was never a slave to his theories and used to say: 'These concepts are subject to change without notice.'

One of Albright's do's was 'obtain financial or other backing which leaves you free to pursue whatever project seems most promising. The man not the project should be endowed.' I do not know whether or not this has ever been possible except with gifts from philanthropists and suspect Albright was being somewhat economical with the truth. He was lucky to have been given free rein and supplied with funds by the departmental boss Dr James Howard Means. He was also lucky to have use of the metabolic research ward at the MGH, one of the first facilities of its kind, that had opened in 1925.

Something Albright avoided was becoming an administrator. His 'do not' number nine was: 'See to it that some fine morning you do not wake up in an executive job. Do not show too much administrative ability. The first time you are asked to serve on a committee, be anything but efficient...whatever else you do, do not become a Professor of Medicine or the head of a department.'

I will end by applying Albright's axioms to the history of diabetes. One person who was protected and allowed to get on with his business was Fred Sanger, who almost single-handedly discovered the amino acid sequence of insulin in 1955. Another was Fred Banting, who was (however grudgingly) given the facilities by Macleod that enabled him to discover insulin. However, Banting – who never gave up hope of making another momentous discovery – failed to heed Albright's do not number nine. In 1938, he described his daily life as follows: 'When I go in I find that it is not a lab but an office. There is a pile of letters to answer, phone numbers to call up, people waiting to have an interview, routine work that must be done. Some person wants me to give him some money, someone wants a signature, someone wants to know what to do about a friend of a great aunt's cousin who has a cancer, or who has gone insane. Someone has a cure for diarrhoea or cancer. Some antivivisectionist damns. Some of the staff are sick or want a raise in salary or want a holiday. Some newspaperman wants an exclusive story. Someone has written an article and they wish it commented upon. Some member of the staff has an idea and they wish to discuss it. Some visitor from China, the USA, England has arrived and cannot visit Canada without seeing the distinguished discoverer of Insulin!'

Fuller Albright developed Parkinsonism in 1936 and by the mid-1950s was so incapacitated that he submitted to an experimental operation. Unfortunately, this led to akinetic mutism, which lasted until his death 13 years later.

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