The Determination of Purine Crystal Structures; An Overlooked Prequel to the Discovery of The Double Helix

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The Determination of Purine Crystal Structures; An Overlooked Prequel to the Discovery of The Double Helix.

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A small but important footnote to Watson and Crick's discovery of the double helix some 65 years ago lives on today in the guise of Dr. June Lindsey and her significant if unheralded role in this breakthrough.

By the middle of the previous century, scientists at Cambridge's Cavendish Laboratory were using the by then well-established technique of X-ray crystallography to study a widening array of complex biological molecules. DNA was then emerging as a strong candidate as the elusive genetic material and, in 1946, the structural analysis of two of its critical purine components were assigned to the gifted graduate student June Lindsey (née Broomhead). Lindsey's doctoral thesis and publications (Broomhead 1948, 1951) detailed for the first time the structures of adenine and the closely related guanine. It was to this work a young James Watson turned in the early 1950's, as he and Francis Crick sought the structure of DNA. Lindsey had not only delineated the physical dimensions of these subunits, but also proposed that the individual molecules were bound to one another in a series of repeating hydrogen bonds. This seemingly trivial observation triggered a critical epiphany for Watson as he worked out how the two strands of linear nucleic acids could be bound to one another.

As the historian Robert Olby writes in *The Path to the Double Helix*, *The Discovery of DNA* "It was then that he (Watson) consulted June Broomhead's thesis. There to his amazement he found a regular pattern of hydrogen bonds between neighbouring adenine and guanine bases at just the right order of distance for packing inside his double helix. All Watson had to do was read the accompanying text to find out which of the several dotted lines in Broomhead's diagrams represented in her opinion hydrogen bonds...." (Olby 1974). In Watson's own words "I was drawing the fused rings of adenine on paper. Suddenly I realized the potentially profound implications of a DNA structure in which the adenine residue formed hydrogen bonds similar to those found in crystals of pure adenine" (Watson, 1968). Looking at Lindsey's work, Watson had realized the hydrogen bonds could serve as the "zipper" for the two nucleic acid strands making up the double helix.

Over the next two days, using cardboard models of the nucleotides based on Lindsey's dimensions, he tried to join the nucleic acid strands, lining adenine up with adenine. Encountering difficulty, he then realized that an adenine hydrogen bonded to a thymine was the same size as the other two constituents of DNA, cytosine and guanine, hydrogen bonded with one another. The two nucleic acids strands could thus be evenly joined, adenines linked with thymines and cytosines with guanines, while satisfying Erwin Chargaff's earlier observation that DNA comprised equal quantities of adenines and thymines as well as of cytosines and guanines (Chargaff 1950). Critically, this model also allowed the two DNA strands to be unzipped and copied, allowing for DNA

replication. Thus, arguably the most transformative discovery in human biology was achieved with June Lindsey's doctoral work playing a central role. As the eminent X-ray crystallographer Durward Cruickshank later wrote of Lindsey's contribution, "it is sad that the famous duo omitted to acknowledge their debt to Broomhead and her colleagues" (Cruickshank 2004).

Lindsey who now lives in Ottawa is both lucid and unsparing in her recollection of that seminal period more than 60 years ago. Counter to today's narrative, it was not Rosalind Franklin (and certainly not herself) but rather her close friend, Edinburgh trained physicist Bill Cochran, who was an unsung hero of the double helix discovery. The self-effacing Cochran derived the complex mathematics required to extrapolate from the "dots on paper" diffraction pattern to the elegant double helix structure, which rather than publishing he merely gave to Crick.

Lindsey would go on to Oxford, where she worked with Dorothy Hodgkin to discover the complex physical structure of vitamin B12 (Brink et al. 1954). In 1951, she arrived in Ottawa with Canadian husband George, a Cambridge physics PhD and polymath himself, one of the inventors of the statistical analysis of baseball known as sabermetrics featured in the film *Moneyball*. She worked at the National Research Council, solving the structures of both morphine and codeine. (Lindsey and Barnes 1955). It was a different time however and the stationing of George to Montreal, a city then devoid of X-ray crystallography, curtailed her science career after a short decade of impressive productivity. This allowed her to keep an eye on the progress of her daughter and son through the somewhat suspect Canadian school system. This was clearly another task at which she excelled, given Jane's position at the Harvard T.H. Chan School of Public Health (research scientist in biostatistics) and Robin's at the University of British Columbia (professor of business management). But with her own stellar and largely unrecognized achievements of almost 70 years ago, June Lindsey blazed a trail for women long before gender equity in science became our era's clarion call.

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