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Secret of Life: Rosalind Franklin, James Watson, Francis Crick, and the discovery of DNA's Double Helix. By Howard Markel. W. W. Norton & Co., 2021. Hardback, pp. 608. ISBN 978-1324002239. Price USD 30.00.

Zygmunt S. Derewenda*

University of Virginia, PO Box 800736, Charlottesville, VA 22908-0736, USA. *Correspondence e-mail: zsd4n@virginia.edu

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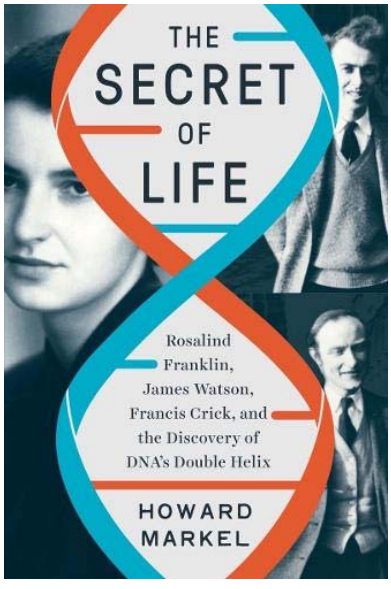

Next April, we will celebrate the 70th anniversary of the proposal for the structure of deoxyribonucleic acid (DNA), the famous double helix. It is one of the most consequential scientific achievements of humankind. The discovery of the double helix was described in three classic back-to-back papers published in *Nature* on 25 April 1953, although only one, purely theoretical – by James D. Watson and Francis H. C. Crick, affiliated with the Cavendish Laboratory in Cambridge, England – is widely remembered today. The others were from two groups at King's College and describe, in highly technical terms, experimental X-ray diffraction studies of fibers of the sodium salt of DNA, the results of which appeared to be consistent with the Watson–Crick model, though not explicitly supporting it. The first authors of the King's College papers were Maurice F. H. Wilkins and Rosalind E. Franklin. Interestingly, the Watson–Crick paper had a footnote:

> We were not aware of the details of the results presented there [in the King's College papers – ZSD] when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

So to a careful reader, there was a model conceived without experimental evidence, and evidence gathered but not brought to fruition in terms of a model. The double helix – as the basis for mechanism for gene replication – initiated a revolution in biology and biomedical sciences. Sadly, Rosalind Franklin passed away in 1958 of ovarian cancer at age 37; four years later in 1962, Watson, Crick and Wilkins were nominated for and received the Nobel Prize in Physiology or Medicine.

This might have provided closure to the story, had it not been for James D. Watson's memoir, *The Double Helix* (Watson, 1968). In it, Watson admitted that Wilkins showed him an X-ray photograph (the now famous Photograph 51) obtained by Rosalind E. Franklin, prior to constructing the model with Crick, and portrayed her in a sexist way. This became the seed for a major controversy. Anne Sayre, Franklin's close friend, published an emotional, defensive biography of her in 1975 (*Rosalind Franklin and DNA*; Sayre, 1975): the Rosalind that Sayre portrays in her book was a very intelligent woman, sensitive and vulnerable, a gifted scientist obsessively devoted to her work, and full of the joy of life when surrounded by friends. The book described a severe clash of personalities Franklin had with Wilkins, and discomfort at the treatment of women, exemplified specifically by the infamous male common room at King's College, a typical Victorian anachronism. Sayre also wrote candidly about Franklin's family history and her Anglo-Jewish, middle-class roots.

Rosalind Franklin, previously unknown to the public, now morphed into an icon of the emerging feminist movement, a woman deprived of her recognition and a victim of misogyny. The discovery of the structure of DNA has since been scrutinized in numerous publications by the protagonists of the story, science historians, authors, journalists, bloggers, and even playwrights and novelists, and is probably the most widely known Nobel Prize winning achievement. In 2002, Brenda Maddox, a writer and biographer who passed away in 2019, used new research for a second, more objective and less emotionally charged biography (*Rosalind Franklin: The Dark Lady of DNA*; Maddox, 2002), but it

did not stop the evolution of a radicalized portrayal of Franklin, often distorting the facts. Neither did the book *My Sister Rosalind Franklin: a Family Memoir* (Glynn, 2012) by Rosalind's younger sister Jenifer Glynn, who came out strongly against false iconization of Rosalind as the tragic heroine, a symbolic victim of the white men's world.

By 2015, Franklin's story made it to London's West End. A play by Anna Ziegler titled *Photograph 51* opened in London, with Nicole Kidman playing Franklin, to rave reviews. This is an excerpt from one of them (Chicago Tribune, 15 September 2015):

> In 'Photograph 51' at the Noel Coward Theatre, Kidman plays Rosalind Franklin, the prodigiously gifted Anglo-Jewish chemist and crystallographer who, at King's College in London in the 1950s, undertook work that led to the discovery of the double helix structure of DNA, key to our understanding of life itself. Franklin's achievements – notably, the X-ray refraction image [sic, ZSD] referred to by the play's title – were seized upon by Francis Crick and James Watson at Cambridge, who, along with her colleague, Maurice Wilkins, went on to Nobel-winning glory. Franklin herself died, aged just 37, from ovarian cancer. Since then, her reputation has been revivified, and the significance of her contribution acknowledged, though the historical details remain disputed. As told by Ziegler, though, this is an account not just of pioneering inquiry, *but of ambition and egotism, of anti-Semitism, sexism and even spite* [emphasis ZSD].

And so the seeds of a conspiracy theory have been firmly planted. Its apogee has now been reached in *Secret of Life: Rosalind Franklin, James Watson, Francis Crick, and the Discovery of DNA's Double Helix* by Howard Markel, MD, PhD. Interestingly, the author himself revealed candidly the motivation that led him to write the book. On 13 September 2021, a week prior to its publication, Markel penned an article for the *Washington Post*, under a provocative title *The ugly truth behind the discovery of DNA: the long-told story behind a critical discovery has erased the crucial role of a pioneering woman*. I quote from the article:

> (...) Franklin was one of the few Jewish women working in postwar British physical science. She was also a pioneer in the emerging fields of biophysics and molecular biology. Yet even as she stormed an ivory tower composed primarily of Christian White men, discrimination against Franklin's gender and the omnipresent antisemitism in British academic circles all but doomed her chance for success.(...) For months, she painstakingly photographed and developed thousands of precise X-ray crystallography films of DNA — from every imaginable angle and focus. She shot tens of thousands of X-ray photos of each specimen, producing hundreds of thousands — if not millions — of data points. And to prove or disprove the molecule's double helical nature, she spent months more, armed only with a slide rule and a ruler, doing the hard math in interpreting her often-contradictory X-ray diffraction results.(...) Then one day in late January 1953, Wilkins surreptitiously showed Franklin's films to Watson, a direct competitor whom he knew to be 'DNA-mad'. When Watson saw the picture labeled Photograph No. 51, his 'pulse raced' and he instantly imagined the double helix of DNA.

Except for the first sentence, everything here is either wrong or, in some cases, at least very misleading. The book thrives on sensationalism based on either ignorance or distortion of facts, and lives up to this preview.

The Prologue begins with an introductory chapter ending with the statement: 'And now it is the time to tell how it really happened'. The claim is unfounded: all the relevant facts have been described before, and nothing new that is of substance is presented. What the book does, however, is to spin facts to fit the narrative of collusion and a conspiracy plot. Part I is intended to set the scene. Chapters 1 and 2 describe the well established, basic history of the work on DNA from Mendel. Chapter 3, rather shockingly, begins with a quote from Hitler [sic], and continues with the history of American eugenics. One wonders immediately if this is to pave the way for the implication that Franklin was a victim of anti-Semitism. In Part II, we are treated to biographical sketches of Crick, Wilkins, Franklin, Pauling and Watson – in that order – up to the point when their lives converge on DNA around 1951. All are derived from previous, well known biographies and autobiographies, with a lot of attention paid to Wilkins' and Crick's failed first marriages. But the most troubling is the incorrect depiction of Franklin's work in Paris, preceding her move to King's College, intended to support a claim that at the time she was one of the world leading crystallographers:

> She toiled as intensely as ever, reveling on the opportunity (...) to *become one of the world's finest crystallographers* [emphasis ZSD]. By painstakingly measuring the sizes, angles and intensities of (...) scattered X-rays and then applying complex mathematical formulae to mapping them, the crystallographer develops a three-dimensional picture of the crystal's electron density (...). The crystallographer must rotate the specimen stepwise through hundreds of infinitesimally different angles over a spectrum of 180 (or more) degrees and take an X-ray picture at each one (...). Every one of these hundreds of thousands of X-ray diffraction patterns was, at the time, measured and analyzed by hand, eye, and a slide rule (...).

Parts III to V retell the story between the summer of 1951, *i.e.* the Naples conference where Watson met Wilkins and heard for the first time about X-ray diffraction studies, to the publication of the *Nature* paper in April 1953. Large portions of this section are extracted from Watson's *The Double Helix*, and editorialized throughout to fit the overall narrative. Towards Part V (p. 385) there is an explicit allegation of a conspiracy against Franklin:

> The double helix collusion scheme was nothing short of a plot of men of mutual interests, cultural beliefs and entitlements. A long trail of conspiratorial dominoes was carefully put in place by the participants long before the Watson and Crick paper was published in *Nature*. How those dominoes toppled one after another with such precision, and the machinations by Watson, Crick, Wilkins, Randall, Perutz, Kendrew and Bragg to conceal the fact that the W-C model was predicated on Rosalind Franklin's data, fits the definition of a conspiracy all too well.

Misconduct by the Co-editors of *Nature*, L. F. J. Brimble and A. J. V. Gale is also implied: 'remarkably, peer review was skipped entirely (. . .)'.

Part VI jumps to 1962 and the Nobel Prize award ceremony for Watson, Crick and Wilkins, explicitly invoking another plot to erase Franklin's name and contribution, and finishes with excerpts from an interview with James Watson, which the author conducted in 2018.

It would be a challenge to address in a short review all the errors and misrepresentations, which this book contains. To begin with, Rosalind Franklin was not a crystallographer. She studied physical chemistry at Cambridge, and while her courses included basics of X-ray diffraction (her notes on the subject survived), she had done nothing in this area until she moved to Paris in 1947, where she was hired because of her prior work for the British Coal Utilisation Research Association. In Paris, she was introduced to X-ray powder diffraction with the primary goal being to estimate how much graphite was present in amorphous coal. Franklin's research papers from that period show blurred X-ray images from coal samples, with a few characteristic rings from powder graphite. The book's description of 'hundreds of thousands of X-ray diffraction patterns' and 'electron density' is an anachronistic absurdity that at best might describe contemporary macromolecular single-crystal diffraction assisted by computers and synchrotrons. It is interesting how the author envisaged processing hundreds of thousands of diffraction patterns with a slide rule.

While Franklin's work had significant impact on coal science, and the understanding of its physical properties, it did not involve any work aimed at structure determination of any compound. However, she gained experience setting up diffraction experiments looking at amorphous, partly ordered material. This is why she was eventually offered a position by Sir John T. Randall, the Director of the Biophysics Research Unit at King's College, London, to study X-ray scattering by protein solutions. Somewhat by serendipity, owing to the intervention by his Deputy, Maurice Wilkins, the project was changed to that focusing on DNA fibers.

Franklin did not need any crystallographic experience when she started the project, because neither A nor B DNA are crystals. Back in the 1950s, Wilkins and others introduced the adjective 'crystalline' in reference to the A form. Looking this up in the Merriam–Webster Dictionary, we find two meanings: (1) 'resembling a crystal' and (2) 'made of crystal'. In the A, or less dehydrated form of DNA, the long molecules are packed closely, so that the sugar–phosphate backbones (but not the bases) show limited three-dimensional ordering. As a result, the diffraction pattern of the A form, resembling in a limited way that of a crystal, shows a small number of Bragg reflections resulting from this phenomenon, confusingly overlayed on a diffuse and weak helical diffraction pattern. The more hydrated B form has the helical molecules farther apart, in the absence of three-dimensional order. The term 'paracrystalline', applied to the B form, is misleading albeit semantically correct: 'paracrystal' is by definition an object with less than three-dimensional order, and B-DNA has no such order at all.

The description of Franklin's work in London, as portrayed in the *Washington Post* preview, is as absurd as the portrayal of her work in Paris. Initially, she focused entirely on the technical aspects of obtaining good quality X-ray diffraction images, with the new equipment that was ordered prior to her arrival by Wilkins. Her fiber photographs required exposures of 50–100 h. Ten thousand such photographs (as the book suggests she took), taken in succession, would have required over 100 years (there was a reason why the photograph is labeled 51: it is its successive number). When Franklin attended the International Union of Crystallography Congress in Stockholm in July of 1951 (where she traveled with Dorothy Hodgkin), she had an opportunity to listen to a lecture by Lindo Patterson, about the method he developed in the 1930s to solve crystal structures. She also listened to John D. Bernal who gave a talk about over interpretation of molecular models, and the need to obtain supporting rigorous experimental evidence. It was only then that Franklin decided to learn and use the Patterson method to attack the A form, given the presence of a limited set of Bragg reflections. As to the 'millions of data points': Franklin's Patterson function calculations used intensities of 66 reflections, since only so many could be indexed. The B form yielded a pure fiber diffraction pattern with no Bragg reflections ('data points').

Although the book is not the first to imply that when Watson saw Photograph 51 he immediately saw the double helix, this is taken to a new level:

> When Watson saw the picture labeled Photograph No. 51, his 'pulse raced' and he instantly imagined the double helix of DNA.

Photograph 51 is an excellent fiber diffraction photograph of B-DNA. As has been clearly documented in many publications, the key to the solution of the double helix was not any of the features of the B form, but the *C*2 symmetry of the A form. By January 1953, Watson – sidetracked for a year by Sir Lawrence Bragg to work on the tobacco mosaic virus – became increasingly knowledgeable about helical diffraction theory, formulated initially by Alexander Stokes at King's and published in an extended form by William Cochran, Francis Crick and Vladimir Vand in 1952. Upon seeing Photograph 51, Watson realized that DNA must be a helix, and that constructing a model must be possible based on the existing chemical knowledge. As Watson stated in 1999, 'It was, psychologically, it motivated us'. Photograph 51 had a profound stimulating effect, but did not lead directly to the double helix hypothesis.

What is not acknowledged in the book is that in the spring of 1953 virtually all information necessary to build the double helix was available from chemical considerations, allowing – contrary to Franklin's presumptions – for informed model building. The work of Alexander R. Todd of Cambridge University (1957 Nobel Prize in Chemistry) established by early 1952 the exact chemical structure of a DNA strand as a linear polymer of nucleotides joined by 3′-5′-phosphodiester bonds. The crystal structures of pyrimidine and purine bases, constituents of the nucleotides, have been known since 1950,

notably from the work of another pioneering woman, June Broomhead, working at the Cavendish Laboratory under Sir Laurence Bragg (she passed away recently in Ottawa, at the age of 99). The relative orientation of the bases and the deoxyribose, and the stereochemistry of the latter, were known from the crystal structure of cytidine, by Sven Furberg in 1950. The interplanar distance between the bases, *i.e.* 3.4 Å, and their perpendicularity with respect to the fiber axis, were inferred from the X-ray photographs by William T. Astbury and his student Florence Bell, in 1938, but confirmed later using spectroscopic methods, by Wilkins among others. Evidence that the bases face inwards, and are linked by hydrogen bonds, emerged from the work of J. M. Gulland and D. O. Jordan in 1947. James M. Creeth, working with Gulland and Jordan, proposed a model of DNA with two chains and sugar–phosphate backbones facing outwards in 1948 in his PhD thesis at University College Nottingham. Several helical models had been built, attesting to the notion that such a structure was thought to be the most probable. Importantly – what is entirely missed by the book – is that the Fischer convention that describes the handedness of chiral molecules like deoxyribose has been proved correct in the absolute sense by Bijvoet in 1951. This is the reason why the double helix was proposed correctly to be right handed; such information could not have been inferred from any fiber diffraction photographs.

Once all this is in hand, the question becomes how the chains are oriented with respect to one another. Francis Crick realized the significance of the *C*2 space symmetry assigned to A form DNA by Franklin, as a result of her meeting with Dorothy Hodgkin (although the fact that the diffraction pattern was consistent with a monoclinic system, and thus had twofold symmetry, was already recognized by Wilkins earlier). This information was obtained by Watson and Crick from the MRC report that Max F. Perutz – Crick's supervisor – showed them, although Franklin reported it in the seminar that Watson attended in November 1951. Again, it is only the data from the 'crystalline' A form that indicate *C*2 symmetry. This, of course, applies only to the pentose–phosphate backbones and not to the bases, which are virtually random in sequence. On p. 323 it is stated erroneously that the *C*2, face-centered, monoclinic space group 'indicates the molecules two-chain complementarity'. Lattice centering has absolutely no significance, and the twofold axis implies the presence of two identical, not complementary, chains. The complementarity arises from the A–T, C–G pairing which was recognized by Watson, who was guided by the edge-on hydrogen bonding in the structures of guanine and adenine published by Broomhead, and by Jerry Donohue's knowledge of the tautomerism of the bases and his insights into hydrogen bonding. No X-ray photographs could even hint at it.

Franklin's words after she learned about the double helix model are well documented: 'We all stand on each other's shoulders'. She did not cry foul, and there is no record of her ever accusing anyone of stealing her data. Perhaps she did not see anything in the model that would have explicitly required knowledge of something only her data showed and that was not disclosed publicly. After Franklin left King's College and became ill, she was on such friendly terms with Watson and Crick that for some time she lived with Crick and his wife Odile. Would she ever do this if she thought they had cheated her?

This brings us to conspiracy theories in the book. The accusation that Watson, Crick, Wilkins, Randall, Perutz, Kendrew and Bragg (*i.e.* six Nobel Prize winners, including one Jewish scientist, and one Fellow of the Royal Society knighted by Queen Elizabeth II) conspired against Franklin before Watson and Crick published their paper, given that there is not the slightest evidence, and that all these men have passed away, is unacceptable. There was no plot on the part of the *Nature* Editors, either. In the 1950s external reviewers were consulted by *Nature* only rarely, and most manuscripts were not sent out for review. This practice continued, to a lesser degree, under John Maddox until 1973.

This brings me to the next conspiracy of 'Christian White Men', one that deprived Franklin of recognition in 1962. It is misleading to imply that the double-helix structure was the sole reason for awarding the Nobel Prize. The structural hypothesis put forward in 1953, was only the beginning of a process, which lead to the 1962 Nobel Prize. The citation reads:

> The Nobel Prize in Physiology or Medicine 1962 was awarded jointly to (Crick/Watson/Wilkins) for their discoveries concerning the molecular structure of nucleic acids *and its significance for information transfer in living material* [emphasis ZSD].

During the nine years since the discovery, dramatic progress was made in the understanding of the genetic code and the way it works. The Central Dogma was formulated by Crick; messenger RNA was discovered by Watson, Brenner and others; the pivotal Nirenberg–Matthaei experiment, a major step in the unraveling of the genetic code, was published in October 1961. Crick, Watson and Wilkins worked on DNA, RNA and the genetic code continuously following the 1953 publications; in contrast, Franklin left King's in March 1953 and for the rest of her career until her death in 1957 worked on viruses, a field in which she made significant advances, and for which she should be remembered. The implicit, or rather explicit, assertion in the book that lectures by the three Nobel Laureates in 1962 deliberately ignored Franklin is again very misleading. Watson and Crick delivered Nobel Lectures which did not even discuss the structure because they had moved on to other exciting developments. Crick's lecture was titled *On the Genetic Code* while Watson's was *The Involvement of RNA in the Synthesis of Proteins*. Each mentions the double helix only once in their lectures. Only Maurice Wilkins, who continued to work on the structure of DNA after 1953, and prior to the Nobel Prize published more than 25 papers on the structure of DNA, RNA and nucleoproteins, gave a talk under the title *The Molecular Configuration of Nucleic Acids*. He did acknowledge Franklin twice in his lecture.

It is of note that many others, who contributed significantly to the discoveries that led to the 1962 Nobel Prize, have not been acknowledged in a more profound way either. William T.

Astbury, the true pioneer of structural biology and biophysics, lay the foundations for the structural characterization of macromolecules with his original fiber diffraction experiments on both keratin and DNA, and opened the door for Pauling, as well as Watson and Crick, who followed up with the α-helix and double helix. Like Franklin, he is mentioned only by Wilkins. In spite of his transformative research, Astbury – who died in 1961 and could not have been nominated a year later – has been nominated for a Nobel Prize only once, by Albert von Szent-Györgyi, in 1953 in Physiology and Medicine. Erwin Chargaff, whose observations were key to both discovery and validation of the A–T G–C pairing, is also mentioned but once by Wilkins; like Astbury, he did not receive a Nobel Prize although he was nominated twice, in 1965 and 1967. He passed away only in 2002.

Franklin joins a pantheon of great scientists who made transformative contributions but for various reasons have not been honored with the Nobel Prize. Some, like Franklin, passed away tragically before their accomplishments could be recognized. These include Henry Mosley (killed in World War I, in 1915) who pioneered X-ray absorption and made critical insights into the Bohr model of the atom; and Richard Abegg, killed in a balloon accident in 1910, who pioneered valence theory and may have overshadowed Gilbert N. Lewis, had he lived. Others never won, in spite of multiple nominations: Gaston Ramon (discoverer of the diphtheria toxin) holds the record with 155 nominations; Emil Roux, the founder of immunology, 115; Arnold Sommerfeld, 84; and Gilbert N. Lewis was nominated 41 times – to no avail.

Finally, I wish to confront the issues of misogyny and anti-Semitism. There is no question that women entering science and academia in the 19th and 20th centuries faced immense barriers – as they regrettably often do now. Regardless of Watson's sexist language in *The Double Helix*, the question is, did Franklin experience misogyny at King's and had such conduct limited her professionally and prevented her from reaching the goal? The science historian Horace Freeland Judson made a specific point of addressing the question of the treatment of women at King's College, and interviewed most of the women who worked there in the 1950s: the conclusion was that in contrast to a generic workplace in those years, women at King's were treated respectfully, regardless of the anachronistic common room, particularly owing to the attitudes enforced by John T. Randall himself. Judson wrote:

> In short, those of Franklin's colleagues at King's who were women unanimously reject the view that her troubles there arose because she was shut out as a woman (. . .). They reject as unhistoric and anachronistic the use of Rosalind Franklin as an emblem for the condition of women in science.

Regarding anti-Semitism, it has been stated in several accounts that Francis Crick did not know in 1953 that Franklin was Jewish. It is not clear that Watson knew at the time and there are certainly no references in *The Double Helix* to her ethnicity. Importantly, this is what Jenifer Glynn wrote in her book:

> This raises the question of Rosalind's Jewishness and whether she ever felt herself to be the victim of anti-Semitism. The simple answer to the second part is 'no' (. . .). There was no restriction on the number of Jews at her schools or her University, many of her closest friends were not Jews, but it happened that many of her closest scientific colleagues were – Vittorio Luzzati in Paris, Aaron Klug at Birkbeck; a high proportion of scientists are (. . .). She was not in any way religious, but Judaism is broader than that, and she always thought of herself as a Jew (. . .). *None of us were ever aware of anti-Semitism in our own lives, never felt we were outsiders with any obstacles to our jobs or careers* [emphasis ZSD].

Jenifer Glynn is the authoritative and conclusive voice.

Secret of Life has several endorsements on the back cover: two are from journalists, but none from a biophysicist with understanding of the field, who would recognize the various errors and bias.

Secret of Life fails to meet the basic standards of science history and disrespects the memory of Rosalind Franklin, fabricating a conspiracy theory that she would abhor. A highly gifted, intelligent woman single-mindedly dedicated to science, she found herself entangled by serendipity in a complicated project. She had made important progress, but did not bring it to closure, for many reasons. Science is conducted now in a different way, and many of the errors and missteps of 1953 would not occur today. On the other hand, scientists are scooped, and embroiled in personal conflicts and competition more frequently than ever. Rosalind Franklin should be remembered primarily for her pioneering and highly successful work on virus structures and training of two extraordinary scientists, Sir Aaron Klug (Nobel Prize, 1982; died 2018) and Kenneth C. Holmes (Fellow of the Royal Society; died 2021). She has indirectly given us Fourier electron microscopy and synchrotron radiation, which brought another revolution in biology.

Rosalind was a brilliant scientist who all her life aspired to have her accomplishments acknowledged by a Fellowship of the Royal Society, and to be remembered for her success. It is unfortunate that all those witnesses who would otherwise come forward to debunk the myth of conspiracy theories relating to her, are no longer with us.

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