Before Watson and Crick in 1953 Came Friedrich Miescher in 1869

Ehud Lamm,*,1 Oren Harman,† and Sophie Juliane Veigl‡
*The Cohn Institute for the History and Philosophy of Science and Ideas, Tel Aviv University, Tel Aviv, Israel 6997801, †Science, Technology and Society, Bar Ilan University, Israel 5290002, and ‡Institut für Philosophie,Universität Wien, 1010 Wien, Austria
ORCID ID: 0000-0003-2980-7847 (E.L.)

ABSTRACT In 1869, the young Swiss biochemist Friedrich Miescher discovered the molecule we now refer to as DNA, developing techniques for its extraction. In this paper we explain why his name is all but forgotten, and his role in the history of genetics is mostly overlooked. We focus on the role of national rivalries and disciplinary turf wars in shaping historical memory, and on how the story we tell shapes our understanding of the science. We highlight that Miescher could just as correctly be portrayed as the person who understood the chemical nature of chromatin (before the term existed), and the first to suggest how stereochemistry might serve as the basis for the transmission of hereditary variation.

If you are a geneticist, you probably do not need to think twice when asked who discovered the molecular basis of all living organisms. You have been taught, along with the rest of us, that it was Francis Crick and James Watson who unraveled the "secret of life," in 1953. But precisely 150 years ago, back in 1869, a 25-year-old Swiss biochemist discovered a new substance in cells, calling it nuclein. It is this substance that is now known as DNA. The biochemist is all but forgotten.

His name was Friedrich Miescher, and if you have not heard of him, you are not alone. Notwithstanding his absence from popular accounts of the history of genetics, Miescher isolated nuclein. He also hypothesized that it may serve as the material basis of heredity. In his later years, Miescher privately intimated that inheritance could be (at least partly) realized by something akin to a code. But when his discovery is mentioned, if at all, Miescher's thoughts about the possible role of nuclein in heredity are invariably omitted. Why he became forgotten to history is likewise left undisclosed.

The aura of the DNA molecule, together with the panache of the two men most associated with the discovery of its structure, helped enshrine an origin story of the birth of molecular genetics that omits the original 19th century discovery of the molecule. This origin story proceeds from the Avery, McCleod, and McCarty experiment of 1944, through the explication of the structure of DNA by Watson and Crick in 1953, through the Meselson–Stahl experiment of 1958, to the elucidation of the genetic code in the subsequent decade, and the ensuing golden age of molecular biology.

Returning to the 19th century and Miescher, however, we are able to trace another story. In this telling, the understanding of the chemical and physical organization of nuclein and associated proteins, now called "chromatin," went hand in hand with the conceptualization of these molecules' genetic significance from the very beginning. Here, we show how the two interlinked concerns were gradually separated by competition between different fields within the life sciences, including cytology, genetics, and biochemistry, obfuscating the early stages of the molecular understanding of heredity. The Miescher episode sheds important light on how genetics became a discipline, illustrating the often tortuous path leading to the acknowledgment of scientific discoveries.

doi: https://doi.org/10.1534/genetics.120.303195
Manuscript received December 17, 2019; accepted for publication March 25, 2020; published Early Online April 6, 2020.
[1]Address for correspondence: The Cohn Institute for the History and Philosophy of Science and Ideas, Humanities Faculty, Tel Aviv University, Ramat Aviv, Tel Aviv 6997801, Israel. E-mail: ehud.lamm@gmail.com

[1]The historical episode discussed in this essay is analyzed by us in detail in Veigl *et al.* (forthcoming).

[2]The relation between classical and molecular genetics, and whether the former can be reduced to the latter became a standard topic in philosophy of biology. An influential paper on the topic is Philp Kitcher's "1953 and All That: A Tale of Two Sciences" (Kitcher 1984). Here, we want to emphasize that the story is just as much about disciplines and methods as it is about the relations between theories. We also wish to point out that the tension began almost a century before the time Kitcher chose to place his focus.

[3]Johannes Wislicenus sponsored the translation of van't Hoff's work into German, in 1876, which together with Hermann Kolbe's 1877 attack on it, drew attention to van't Hoff's ideas [see Riddell and Robinson (1974) and Drayer (2012)].

[4]Wilhelm His Senior (1831–1904) invented the microtome, and, among other things, discovered neural crest cells.

It likewise exemplifies the wide range of factors, within and beyond science, that affect the fate of scientific ideas.[1]

Miescher's Context of Discovery: On the Reception of "Nuclein"

Johann Friedrich Miescher was born in 1844 in Basel, Switzerland. Both his uncle, Wilhelm His, and his father, Friedrich Miescher senior, were famous physicians who taught at the University of Basel. After completing his medical studies, Miescher joined Felix Hoppe-Seyler's renown "Schlosslaboratorium" in Tübingen, Germany. Hoppe-Seyler was known for his work on hemoglobin and is considered the founding father of "physiological chemistry," a discipline that transformed over the years into what we now call "biochemistry." His student, Miescher, was determined to learn about the fundamental properties of all living organisms and chose to work on a topic of his own: the chemical composition of the nucleus (His 1897a; Jaquet 1944).

Work conditions were less than optimal, calling for creative solutions. Miescher harvested nuclei from pus cells in used hospital bandages. Even after becoming professor in Basel, he would toil in freezing temperatures, with laboratory windows kept open to avoid deterioration of material extracted from salmon sperm obtained from Basel's weathered fishermen (Hughes 1959).

From the hospital bandages, Miescher digested the lymphocytes with proteases, shook them over an ether/water solution, washed them with warm alcohol, treated them with alkaline solution, and precipitated a substance by adding acid, which he considered to be novel based on its composition of elements. Miescher concluded that this substance was located in the nuclei of cells and determined that the substance he found was not a protein; rather, it was a new substance, principally due to its high concentration of phosphorous. He concluded that his isolate was heretofore unknown, christening the substance "nuclein," as it could only be precipitated from nuclei (Dahm 2005, 2008).

It would take 2 years until Miescher's discovery was published, in 1871 (Miescher 1871). In an exchange early career scientists may identify with his mentor Hoppe-Seyler, the latter agreed to publish the results in his journal, *Medicinisch-Chemische Untersuchungen*, but only after he had two other students replicate and verify them. Pál Plósz and Nikolai Nikolaevich Lubavin performed careful experiments following Miescher's protocol, and found nuclein-like substances in casein (Lubavin) and blood (Plósz). Both treated their substrates first with proteases and then performed the extraction, obtaining a substance that was not soluble in acids but soluble in alkali (Plósz 1871; Lubavin 1871). Well aware of its meaning for his own claims to priority, Miescher insisted that a note be published alongside his paper explaining the delay. Committed to publishing empirical findings rather than opinion pieces, Hoppe-Seyler nevertheless refused to publish Miescher's speculations about why different researchers had found (slightly) different chemical compositions of nuclein (His 1897b). The refusal, as we shall see, would contribute to fostering distrust in Miescher's discovery.

As it happened, the real reason for the delay from 1869 to 1871 was that Hoppe-Seyler wanted to avoid repeating an earlier scandal. A few years before Miescher, Otto Liebreich, another of Hoppe-Seyler's students, claimed to have isolated a novel substance he called "protagon" from brain tissue (Liebreich 1865). And while Hoppe-Seyler continued to acknowledge his student's discovery, the reality of the substance was cast into doubt by the German-born British surgeon and biochemist Ludwig Thudichum, sparking a debate in Great Britain that left researchers suspicious of so-called "new" substances, especially from a Hoppe-Seylerian origin (Fruton 1990). After Hoppe-Seyler and his students individually precipitated nuclein from different substances, Hoppe-Seyler was ready to publish; however, the Franco-Prussian war further delayed publication.

Following the eventual publication, Miescher became Professor in Basel at the age of 28, in 1872. He was a tireless worker: Miescher's student Fritz Suter relates how his boss did not appear at his own wedding, and was found instead in the laboratory. On another occasion, when the laboratory ran out of glassware for experiments, Miescher used his own Sèvre dinnerware (Suter 1944). But Miescher soon turned from nuclein to other topics, including the development of egg and sperm, respiration, and circulation, as well as the nutrition of inmates in Switzerland (a task he was not especially thrilled to undertake). He would end his career having published only a handful of scientific papers, conspicuously including two papers about the mysterious denizens of the nuclei of cells (Miescher 1871, 1874).

In the following decades, a debate raged about whether nuclein was indeed a novel substance or an experimental artifact. The inconsistencies concerning the chemical composition of nuclein served as a major stumbling block for the claim of novelty. In his unpublished commentary, Miescher had argued that the replication performed by Hoppe-Seyler was in fact robust: slightly different methods brought about slightly different results, yet the major findings were consistent with his own. This view was not shared by his critics, however. While he argued that a good replication involves protocols that are modified slightly to avoid similar biases, others saw the resulting discrepancies as evidence for the dismissal of nuclein as a genuine substance (Kingzett and Hake 1877; Kingzett 1878; Thudichum 1881). Such disputes are common in science: if experiments are replicated in exactly the same conditions, it can be argued that the replication was subject to the same biases. Conversely, if experiments are replicated in slightly different conditions, it can be argued that this was not a "real" replication (Collins 1992). Many of Miescher's critics were French and British, and memories of the Franco-Prussian war were yet fresh (Geppert and Gerwarth 2008). In such times of distrust, replication did not prove sufficient to resolve the scientific debate.

Simultaneously to the debate about nuclein's validity, Miescher made a second discovery. Realizing that nuclein was typically found in conjunction with other substances, he concluded that such so-called "contaminants" were in fact proteins. Miescher determined the chemical make-up of these contaminates and coined the newly discovered protein "Protamine." Having determined that nuclein is acidic, in 1871 he coined the association of the two substances, "nuclein-acidic protamine" [published in Miescher (1874)].

But Miescher's term did not stick. Miescher was a chemist, whereas cytologists, whom he disparagingly referred to as a "guild of dyers," considered themselves the experts on what resides within cells (His 1897a). By staining cells with aniline, the German cytologist Walther Flemming consequently identified a structure in the nucleus that absorbed basophilic dyes a full decade after Miescher's discovery, coining it chromatin in 1882 (Flemming 1882). The term chromosome was introduced 6 years later, in 1888, by Flemming's colleague at the University of Kiel, Wilhelm Gottfried von Waldeyer, to refer to the loops of chromatin that he observed (Waldeyer 1888). Although it was known that they played a role in cell division, the precise significance of these entities for genetics remained unclear. In what may well have been the aftermath of the transnational dispute regarding nuclein, Miescher's nuclein-acidic protamine had never been picked up by his peers.

It was a time of major advances in biology. Already in 1875, the brothers Oscar and Richard Hertwig had elucidated fertilization, buttressing cytology's claim to be the queen of the cellular sciences (Hertwig 1875). In 1881, the young botanist Eduard Zacharias managed to show through staining that nuclein colocalized with chromatin (Zacharias 1881). Zacharias used Miescher's extraction method and combined it with staining. When he treated plant cells with proteases he could still stain for chromatin, but if he treated the cells with proteases first and then with alkali, which dissolved nuclein, no staining was possible (Zacharias 1881). Coining and defining chromatin in his groundbreaking 1882 book, *Zellsubstanz, Kern und Zelltheilung*, Walther Flemming wrote "[p]ossibly chromatin is identical with nuclein, but if not, it follows from Zacharias' work that one carries the other."

The second half of the 19th century saw a surge in interest in the nucleus among researchers. After the publication of Charles Darwin's *On the Origin of Species* in 1859 (Darwin 1859), Ernst Haeckel had proposed as early as 1866 that the nucleus was home to the factors responsible for the transmission of hereditary traits (Haeckel 1866). Following Flemming's own aforementioned coining of the terms chromatin (Flemming 1882) and "mitosis" (Flemming 1879), in the late 1880s Theodor Boveri began to suggest that individual chromosomes in fact carry different parts of the hereditary complement, with each chromosome representing a unique repository of the previous generation's traits (Boveri 1888, 1892). But Haeckel's suggestion was more theoretical than empirical, and Boveri's work appeared appreciably later. In the interim, Miescher became convinced that the presence of nuclein rendered the nucleus uniquely different from the cytoplasm, even suggesting in an unpublished addendum to his 1871 paper that nuclei should be defined by the presence of nuclein rather than by morphological properties, since nuclein is implicated in their physiological function (Miescher 1870). He clarified this association to a greater degree in a second publication, in 1874, in which he expressed his own nascent ideas about heredity while establishing the relation of nuclein and protamine. In the paper, Miescher stated:

If we want to speculate that a single substance... is the specific cause of fertilization, then one needs to consider nuclein without doubt. Nuclein has constantly proven to be the main component (Miescher 1874).

With the term "main component" Miescher was referring to the fact that nuclein was ubiquitous in the heads of spermatozoa (Miescher 1874).

How Miescher and DNA Parted Ways

Miescher was unhappy about the reception of nuclein. Already, in 1872, he wrote to his mentor Felix Hoppe-Seyler that he should never have published on nuclein, thereby exposing it to "the mob" (His 1897a). While it was first his fellow chemists who debated whether nuclein was a genuine substance, the interest of the "guild of dyers" irritated Miescher even more. For even with their best lenses, they were unable to detect the structures that he described by chemical analysis. The claim by cytologists that there is "nothing but chromatin" annoyed him (His 1897a), not least due to the fact that they had not even picked up on his terminology, differentiating nuclein, protamine, and nuclein-acidic protamine. Miescher was therefore aware of cytological findings that vindicated the role of the nucleus in heredity, but did not engage with the cytological community due to his methodological proclivities, his disdain for the microscope, and the fact that cytologists refused to adopt his terminology.

The relations between the newly emerging biological chemistry and cytology were complicated. It was unclear which methods would ultimately lead to better understanding of the processes of life, nor was it certain whether and how their results could be integrated. It remains an historic irony that the cytologists were the ones who appreciated the discovery of nuclein and investigated its relation to chromatin, albeit not in conversation with Miescher himself, while chemists debated whether nuclein was an experimental artifact.[2]

The "guild of dyers" were not the only ones upsetting Miescher for not sticking with his terminology. The German pathologist and histologist, Richard Altmann (1852–1900), argued in 1889 that nuclein should always refer to the mixture of nucleic acid and protein, and the term nucleic acid should denote the substance cleaned of all proteins. This nomenclature was precisely the opposite of Miescher's. His nuclein was taken to be Altmann's nucleic acid, whereas his nuclein-acidic protamine became Altmann's nuclein (Altmann 1889). Miescher was not amused. Miescher wrote in a letter to his uncle Wilhelm His, "My salmon nuclein is, of course, identical with his nucleic acid, and it is the purest of all" (His 1897a). It was Miescher, after all, who lent Altmann the salmon sperm for his experiments.

Considered from the perspective of research on nucleic acids, Miescher's first nuclein was understood to be impure DNA; the impurities had to be overcome to avoid confusion. As this story became the standard one going into the 20th century, Miescher's name and his discovery of nuclein survived, but only as a footnote to the elucidation of DNA by subsequent researchers. The alternative framing, the one highlighting Miescher's realization that nuclein-acidic protamine consisted of acidic nuclein and protein components, became harder to articulate after Altmann's terminological amendment.

We might ask anachronistically: Was Miescher a good chromatin researcher, or a sloppy DNA researcher? Both options are of course misleading, since the relation between the three entities we distinguish today—DNA, histones/protamines, and the cytologists' chromatin—was far from self-evident when Miescher first isolated nuclein. Still, Miescher was the first to work on separating the chemical components of the nucleus. He even made use of his ideas regarding the relation of protamine and nuclein to develop an extraction method: Miescher used protamine to precipitate nuclein in a number of probes (His 1897b). It is worth noting that Miescher did this before chromatin was named; explaining what he discovered therefore requires using terminology that was only developed after his discovery was made.

The distinction between work on nuclein and chromatin reflects the use of different methodologies, but also disciplinary boundaries, with cytology, biochemistry, and finally, genetics vying for supremacy. Writing in 1965, 3 years after Watson and Crick were awarded the Nobel Prize and at a time in which cytology no longer commanded the prominence it once enjoyed, the geneticist Bentley Glass argued that "Miescher had the esteem of his fellow chemists... but the growing army of cytologists and geneticists, who had most to learn from Miescher's work, passed him by" (Glass 1965).

In subsequent accounts on the history of DNA, Miescher morphed into a "confuser," someone whose ideas, rather than his techniques, were deemed misguided. The claim now became that Miescher's early work on nuclein led subsequent researchers to fruitlessly search for a metabolic link between proteins and nucleic acids (Olby 1974). This turn in the historical memory of Miescher highlights a discontinuity in the theoretical understanding of nuclein's role in heredity, brought about by the working out of the genetic code, while concealing a continuity of methods (Levene and Bass 1931). Miescher's original protocols, refined over time, were used by subsequent researchers. Richard Altmann, for example, only used a slight modification to Miescher's protocol (Altmann 1889), a "lucky catch," in Miescher's opinion [Miescher in His 1897a]. While the view on nuclein as a new substance (whether it was metabolically related to proteins and whether it played a role in heredity) shifted over time, the extraction methods persisted throughout the 19th century.

There is of course no single reason why Miescher is all but forgotten. While we believe that disciplinary turf wars account prominently for Miescher's ensuing reception, we wish to point out another factor. Miescher's thoughts regarding the role of nuclein in heredity may not have penetrated the discourse of his peers, but his methodology for isolating nuclein enjoyed a strong continuous run until quantitative analysis through hydrolysis was introduced in the beginning of the 20th century. Renown chemists like the aforementioned Richard Altmann and Nobel laureate Albrecht Kossel (who was also one of Hoppe-Seyler's students) only made small changes to Miescher's extraction method. In molecular biology, we often witness how inventors of famous and widely used techniques are either not known or remain unacknowledged by those using the techniques (*e.g.*, Fisher 2015). One reason for this phenomenon is that successful techniques and the context in which they were developed become "black boxed" once they are established (Latour 1987). A kind of positive feedback dynamic is involved: the success of these methods overshadows their founders, and, when detached from their contextualized histories, the methods enjoy an easier trajectory. Blackboxing Miescher's extraction method might therefore have been a feasible strategy to set it apart from the transnational dispute surrounding nuclein, and the disciplinary turf wars that followed.

The "Code" Before the Code

In the years following the initial publication on nuclein, a key chemical idea was introduced, one that Miescher, a chemist at heart, quickly applied to his conjectures concerning nuclein's role in heredity. Stereochemistry had its origins in observations by Louis Pasteur about the optical properties of organic compounds made in 1848, several years before Miescher's discovery of nuclein. But key developments were made in 1874 when Joseph Achille Le Bel in France and Jacobus Henricus van't Hoff in Holland independently proposed theories of the three-dimensional structure of organic molecules. Van't Hoff defined the notion of an asymmetric carbon (*asymmetrisch koolstof-atoom*), an idea that caught Miescher's attention.[3]

In 1892, just 3 years before his death, and a decade following Charles Darwin's, Miescher raised novel speculations about the role macromolecules played in heredity in a private letter to his uncle, the prominent anatomist Wilhelm His.[4] Referring to a "provisional hypothesis" introduced by Darwin in 1868 to explain how traits might be passed on from one generation to the next, Miescher wrote:

To me the key to the problem of sexual reproduction is to be found in the field of stereochemistry. The gemmuli of Darwin's pangenesis are equivalent to the manifold asymmetric carbon atoms in organized substances. These carbon atoms can alter their stereochemistry through the smallest reason or exterior stimulus, through which mistakes in their organization start to occur. Sexuality is a measure to correct those inevitable stereochemical mistakes in the structure of organic substances. Left-handed coils are restored by right-handed coils, and the equilibrium is restored. In the huge molecules of albumen compounds or in the yet more complicated molecules of hemoglobin, *etc*., the many asymmetric carbon atoms provide a colossal amount of stereo-isomerism. There is a great amount of possible asymmetric carbon atoms and thus also stereoisomers, therefore all richness and variety of hereditary transmission can be expressed equivalently well as can be all words and terms of all languages in the 24–30 letters of the alphabet. It is therefore quite superfluous to make the egg and sperm cell a storehouse of countless chemical substances each of which carries a particular hereditary quality (the Pangenesis of de Vries). My own research has convinced me that the protoplasm and the nucleus, far from consisting of countless chemical substances, contain quite a small number of chemical individuals (compounds) which are likely to be of a most complicated chemical structure (His 1897a).

In modern terms, Miescher was suggesting that macromolecules can store hereditary variation through stereochemistry. Miescher's speculations are not enough to conclude that he had a picture of a mapping from distinct, nonoverlapping parts of nuclein to specific amino acids, as we would later come to realize existed when the genetic code was elucidated. Nor did Miescher explicitly mention nuclein in this letter, referring rather to his research on the compounds of the nucleus (which he believed to almost entirely consist of nuclein and protamine). Nevertheless, it can be plausibly suggested from our own vantage point and using our own terminology, that when Miescher tied "a colossal amount of stereo-isomerism" on the one hand to the expression of "all richness and variety of hereditary transmission" on the other, he was in fact proposing that heredity should be considered in terms of storage and transmission of information, that information is about distinguishing between alternatives, and that information in one domain can be encoded using another.

Miescher's private thoughts about the role of stereochemistry in heredity were never incorporated into a published paper, and historians of biology have often treated them disparagingly, in essence as an insignificant side note (Olby 1969, 1974; Mirsky 1968). This framing seems to agree with how some rendered the relations between genetics, cytology, and biochemistry. The historian of genetics Robert Olby argued that Miescher "resented the cytologists' introduction of fresh levels of organization in open defiance of the biophysicists' programme of reducing physiology to the molecular level" (Olby 1969), the "fresh levels of organization" being critical for classical genetics. Similarly, Ernst Mayr, a key architect of the Modern Synthesis in evolution who was deeply concerned with the autonomy of biology in relation to the "lower level" sciences, claimed that "Miescher never looked at [nuclein] as a carrier of genetic information" (Mayr 1982). Mayr felt that to understand how a seemingly simple molecule like DNA carries the information necessary for control of the development of the organism required understanding the "exact structure of DNA," something Miescher never achieved (Mayr 1982). Clearly, Mayr's conclusions are weakened by recalling Miescher's speculations about stereochemical encoding of hereditary variation in 1892, and the extent to which such speculation depended on the development of stereochemistry, which occurred between Miescher's initial discovery of nuclein and his later unpublished speculations. Moreover, these speculations, reminiscent as they are of genetic information, point in the same general direction in which Mayr himself and others would later find the autonomy of biology. Olby's assessment is also perhaps too quick when we recall that it was the cytologists who embraced nuclein. Social historians of science would in later years argue that the metaphor of "information" would only become possible in biology once the "information age" had arrived, care of Bell Labs and the transistor, and the early computers developed by IBM (Kay 1995, 2000). Like Olby and Mayr before them, they too would rewrite historical memory, leaving little room for Miescher.

Conclusion

Miescher died of tuberculosis in 1895, at 51 years of age. In the last 2 years of his life he was unable to continue his work due to deteriorating health, attempting to recover from his disease at a sanatorium in Davos. He was married and had three children, all of whom died at a young age, leaving him no direct descendants.

History of science all too often highlights "superstar" scientists who have illustrious careers, overcoming great obstacles and resistance to new ideas, leading to a public vindication, sometimes followed by a Nobel Prize. Miescher's story is different. There was no immediate recognition nor ultimate vindication in his case, yet his discovery proved fundamental for the whole of modern biology. Excavating stories such as his from the past, and incorporating them into the history of genetics, helps us portray the process of science more realistically.

Indeed, whether Miescher is best remembered as the discoverer of DNA or chromatin is probably not important. More relevant are the ways in which his story both illustrates and challenges the thesis of the social construction of science and of its history (Fleck 1935). That Miescher has all but been written out of the history of genetics teaches us that we have come to think that the story about the molecular representation of hereditary information started more than half a century later than it really did. The fashioning of historical memory corresponds to the fashioning of science itself, often because the history of science is written by, and influenced by, its practitioners. Miescher was forgotten, in many respects, due to the large role played by disciplinary disputes in fashioning the landscape of biology. This is a good example of how social, rather than purely intellectual, factors play a role in how science is both practiced and remembered.

Yet, with the help of Friedrich Miescher and the reception of his discovery, we can better comprehend how the history of genetics consists of two strands: DNA and chromatin; information and physiology, intertwined, twisting around each other, from 1869 until the present. Indeed, in the standard story of genetics ossified during the heyday of DNA and the genetic code, Mendel was cast as a father figure, and the understanding of the cell cycle by cytology was relegated to a side story, with chromatin becoming relevant again to genetics only decades later. But Miescher's notion of stereoisomers as potentially constituting a kind of alphabet, in an unpublished letter to his uncle Wilhelm His, argues for the possibility of thinking of storage, transmission, and encoding of information well before such terms existed in the broader culture in which science is situated.

Miescher may have been written out of the history of genetics due to clashes between disciplines, but he also came up with a notion of heredity scarily close to our own, more than two generations before the dawn of the "age of information." It was patently possible therefore to imagine an hereditary alphabet based on stereochemistry, long before the world became suffused in bits and bytes. These, in turn, may indeed have helped grow a metaphor which would take over biology in due course.

Acknowledgments

This research was supported by Israel Science Foundation grant 1128/15 to O.H. and E.L. and Austrian Science Fund grant W 1228-G18 to S.V.

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Communicating editor: A. S. Wilkins