

Everlasting Bio-Chemistry and Genomic analysis

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Abstract:

This personal essay highlights selected developments in the early history of molecular biology. Molecular biology in nature has been around whether as a result of chemical evolution on Earth or having been imported from elsewhere as supposed by panspermia. Molecular biology in science was emerging in the 1930s. In 1938, Warren Weaver (1894–1978) coined the name “molecular biology,” and this is why this date is often referred to as its beginning [1]. Weaver did much more than coining a name; as a division head at the Rockefeller Foundation, he facilitated support for budding research directions.

Keywords: pathological, molecular biology, biology researchers.

INTRODUCTION:

At about that time, the pioneering thought occurred to Linus Pauling (1901–1994) that pathological conditions might be caused by events at the molecular level and alleviating them might be possible by what he called molecular medicine. His stellar achievement was the alpha-helix structure of proteins that he discovered in the late 1940s. The pace of research was rather slow and there was hardly any competition. In the 1950s, the situation would markedly change.

In 1935, three German scientists published a paper in which they concluded that inheritance may be connected to molecular systems, considering the thermal stability at around 37 degrees Centigrade of the human organism [2]. Their treatise was revolutionary because of this suggestion and because it was unusual at that time for biologists and physicists to join forces for solving scientific puzzles. This treatise might have disappeared into oblivion if Erwin Schrödinger (1887–1961) had not resuscitated its conclusions in his book *What is Life?* 80 years ago [3]. As Schrödinger hinted at the possible need for discovering new physical laws for understanding life, some already established scientists and many more budding researchers turned to biology in quest for those new laws.

The noted physicist Leo Szilard (1898–1964) did not need Schrödinger’s challenge to recognize that the next frontiers of science might be in biology as early as some time before World War II. However, circumstances fast changed his direction of action. His prophetic vision in nuclear physics predicted the possibility of nuclear chain reactions with its horrific implications. He realized that he had to stay in nuclear physics and nuclear weapons to help averting the growing menace of Nazism. He stayed with it until after the war ended and only then switched to biological research.

Francis Crick (1916–2004) was one of the younger scientists who changed from physics to biology after World War II. He found his scientific home at the Cavendish Laboratory in Cambridge, England. Pivotal changes were taking place there at the time. W. Lawrence Bragg (1890–1971), the Cavendish Professor of Physics, realized that staying at the forefront in science would not suffice to take rearguard actions in atomic physics. He boldly went ahead and steered the Cavendish into two new directions. One was radio physics and the other, molecular biology. Eventually both paid off with spectacular successes. The latter would develop into the Laboratory of Molecular Biology, a world leader in the field [4]. It is instructive to remember how it had started, and there was no single big decision and spectacular announcement. Rather, it was born in 1947 through unassuming informal exchanges between Sir Lawrence and Edward Mellanby (1884–1955), the head of the British Medical Research Council (MRC) to take the unusual step for this medicinal institution to support a project at a physical laboratory.

This X-ray crystallographic study of the structure of protein molecules. In Bragg’s words: “If we can get into a quiet corner for five minutes, I think I can explain what it is all about and find out from you how to frame our actual request for money” [5].

From left to right: Oswald T. Avery, 1948. Courtesy of Maclyn McCarty; Erwin Chargaff, 1994, in his home in Manhattan; and Frederick Sanger, 1997, in Cambridge, UK. The latter two photographs by Istvan Hargittai.

Lately, I have met with the notion that molecular biology is not a branch of science; rather, it is a collection of tools, and as branches of science go, molecular biology had given its place to systems biology. It is indeed a legitimate question whether molecular biology is more of a collection of tools or is it, rather, based on concepts. Hopefully, the present sketch about its beginnings demonstrates it is both, cannot one be placed above the other, and the two aspects have progressed in unison. An example: when understanding the genetic code made it an absolute necessity to determine the sequence of amino acids in proteins, the premier researcher of the field, Frederick Sanger (1918–2013), could work it out due to the progress in chromatography [6].

The painstaking experimental work by Oswald T. Avery (1877–1955) and his two associates, Colin M. MacLeod and Maclyn McCarty, led to the concept of the DNA being the carrier of heredity in 1944 [7]. It was almost a “premature” discovery, as most of the scientific community was not yet ready to accept it. It was not easy to brush off the vocal opposition by Alfred Mirsky that even an “insignificant” protein contamination could have misled Avery et al. in making their conclusion. The long-held view about the DNA being a dull molecule as “evidenced” by Levene’s tetranucleotide hypothesis was deeply rooted in scientific thinking [8]. However, the limited impact of Avery et al.’s discovery was not at all insignificant.

Fundamental Details:

Erwin Chargaff (1905–2002) was one of the few scientists whose research direction was profoundly influenced by the new knowledge about the significance of DNA in life processes. He had already become an internationally recognized scientist when he cleared his desk of all his ongoing projects and switched to studying DNA. In this, the recently emerging chromatography proved indispensable. Chargaff made two fundamental discoveries. One was that the DNAs of different organisms were different. The other was the base equivalence. The process that led to this latter discovery was especially noteworthy. A pattern seemed emerging, however hesitantly, from the raw data. The total amounts of the purine bases and the total amounts of the pyrimidine bases in terms of mole quantities appeared to be the same. What was even more extraordinary that the ratios of adenine to thymine and guanine to cytosine, again in mole quantities, were close to one. However, the ratios scattered considerably about one, in some cases, up to about 30%! It took a great deal of contemplation to decide that there was indeed a pattern and a great deal of courage to come out with it publicly. In his 1950 review, Chargaff wrote: “It is noteworthy—whether this is more than accidental, cannot yet be said—that in all desoxyribose nucleic acids examined thus far the molar ratios of total purines to total pyrimidines, and also of adenine to thymine and of guanine to cytosine, were not far from 1” [9]. Three decades later, he noted: “I felt a great reluctance to accept such regularities, since it had been impressed on me that our search for harmony, for an easily perceived and pleasing harmony, could only serve to distort or gloss over the intricacies of nature” [10]. Yet Chargaff could not help but notice that “there emerged—like Botticelli’s Venus on the shell, though not quite as flawless—the regularities that I then used to call the complementary relationships and that are now known as base pairing” [10]. Chromatography as a tool played a decisive role in establishing Chargaff’s two fundamental concepts.

Eugene P. Wigner with Istvan Hargittai, 1969, in front of the old physics building at the University of Texas, Austin. By unknown photographer.

The process of how the discovery of base equivalence happened is a beautiful example of what Eugene P. Wigner (1902–1995) said about the scientific method in his two-minute speech at the 1963 Nobel Prize ceremony: “... science begins when a body of phenomena is available which shows some coherence and regularities, that science consists in assimilating these regularities and in creating concepts which permit expressing these regularities in a natural way” [11]. He talked about this in more detail in his Nobel lecture from which I single out one sentence only. It reads as if the conclusion of the previous quote: “The regularities in the phenomena which physical science endeavors to uncover are called the laws of nature” [12]. During my year as a research associate at the physics department of the University of Texas at Austin in 1969, Wigner came for a one-week visit and he spent one hour every day with me before his official program. Our interactions by correspondence dated back to my student time. Now, he tutored me in symmetry and in more general issues of science, giving me a life-time gift. What I learned from him was that there were no separate physical laws that would have to be uncovered for understanding life that Schrödinger had implied.

ssame token, molecular biology is as smoothly embedded in the body of science as any other branch.

Left: Francis Crick, 2004, in the Cricks’ home, La Jolla. Photograph by Istvan Hargittai. Right: James D. Watson with Istvan Hargittai, 2010, in the Watsons’ Manhattan home. Photograph by and courtesy of Magdolna Hargittai.

James D. Watson (b. 1928) and Francis Crick’s suggestion of the double-helix structure of DNA was a triumph of blending tools—provided information with the conceptual approach of modeling. As I alluded to this above, the notions of “tools” and “concepts” are not as distinguishable as they might sound. For example, X-ray crystallography, a profoundly fundamental tool of molecular biology was born because of testing the concepts of the wave nature of X-rays and the ordered atomic arrangements in crystals. Modeling of biological structures may be considered as much as a tool as a concept. There are ideas that become justified and meaningful much later than when they had been pronounced. A case in point is Schrödinger’s “aperiodic crystal” in which we recognize the DNA molecule to carry the information of heredity, a role that was not yet recognized at the time. To Schrödinger, a small molecule would be an initial seed for the gene. Its extending by mere repetition – the way a crystal is being formed – could not lead to the gene because periodicity would exclude carrying information. The other way for extending the initial seed molecule would be building up a complex organic molecule – we might add that proteins could be such systems, or DNA as we know it today.

DNA and RNA molecules:

There is variety in the biopolymer. Based on this, Klug deduced that comprehending the structure of a biopolymer required recognizing nucleation, or the original seed. He discovered it illuminating to demonstrate how the thought had evolved since he did not instantly arrive at the correct concept. The editor requested that he remove the graphic showing Klug's initial concept of nucleation when he was preparing to publish his Nobel talk [13]. Its inclusion demonstrated a scientific method in obtaining the truth, even if Klug acknowledged that it was incorrect in detail. The famed Principia Mathematica coauthor Bertrand Russell and philosopher Alfred N. Whitehead (1861–1947) were cited by Klug as saying: "It is more important that an idea be fruitful than that it be correct." George Gamow's (1904–1968) groundbreaking exposition of what is now known as the genetic code was a stimulating and innovative move to pose this subject and acknowledge its importance, but I have noticed several negative remarks mentioning it. When asked about the "genetic code," Francis Crick said it was "the key to molecular biology, because it shows how the two great polymer languages, the nucleic acid language and the protein language, are linked together" [14]. Many people have used the phrase "genetic code" to refer to two distinct but related ideas. A genome is a collection of DNA and RNA sequences that code for the proteins and RNA molecules that enable all living things to exist in the natural world. Codons, which are units of genetic code in DNA and RNA molecules, are defined as sequences of three nucleotides; this definition is in agreement with that definition. The second use is to explain the algorithm or key that converts the many genetic instructions into protein amino acid sequences. It would be most appropriate to call this the "genetic cipher" [15]. This lines up with what Crick proposed, who called the decoding method the translation rule and believed it should be called the "genetic cipher." That "genetic code" sounded more interesting than "genetic cipher" was a blessing, as Crick put it, since he "did not know this at the time" [16]. But the old word stuck, and ever since then, everyone from molecular biologists on down has used it to describe the process of translating nucleotide sequences into amino acid sequences. Despite the varied nature of this cartoon, it is crucial to note a bizarre element of molecular biology's early history while considering its origins. In the 1920s, genetics was a rapidly expanding and well acknowledged scientific field in the Soviet Union; but, by the 1930s, things had changed dramatically. During the "Great Terror" of Soviet dictator Iosif Stalin, the renowned geneticist and biologist Nikolai I. Vavilov (1887–1943) was subjected to a series of harsh measures, including the removal of his prominent positions within the Soviet scientific community, a travel ban, an arrest, a prison sentence, and finally, the death penalty due to starvation [17]. The authoritarian actions of the charlatan Trofim D. Lysenko (1898–1976) were the main reason genetics was stigmatized as a non-science discipline and its researchers were degraded, harassed, and even killed. After WWII, during the 1948 conference of agricultural science, all of this picked up steam.

Conclusion:

When Stalin was finally overthrown in 1953, and his atrocities were finally (mostly) exposed in 1956, things began to improve. Oddly enough, Nikita Khrushchev, the newly installed Soviet leader, was just as captivated by Lysenko's repeated assurances that his ideas will revolutionize biology, thus the dictator remained in power for quite some time.

would revive Soviet farming after decades of stagnation. The scientific community benefited from the political "thaw" that occurred during this time. Because of this, the Fifth International Congress of Biochemistry, a major international gathering, could take place in Moscow in 1961. A portion of the conference titled "biological structure and function at the molecular level" was arranged by renowned Soviet scientist Vladimir A. Engelhardt (1894–1984). Molecular biology, which the Soviet government still despised, went under this codename. After some more time had passed, Engelhardt finally gained permission to call his research group the Institute of Molecular Biology within the framework of the Soviet Academy of Sciences [18].

It was a shock that the 1961 Moscow conference could ever happen. Next, a groundbreaking finding was announced, even though the scientific substance was not highly anticipated. An obscure colleague of the then-unfamous National Institutes of Health, Marshall Nirenberg (1927–2010) revealed the initial breakthrough in deciphering the genetic code [19]. Naturally, everyone is familiar with the remainder of the narrative.

The history of molecular biology is an ongoing and ever-evolving tale. With its debut, Academia Molecular Biology and Genomics highlights the need of improving platforms for sharing updates and hopes for the field's future.

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