

1

A Brief Review of the Early History of Genetics and Its Relationship to Physics and Chemistry

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Physicists and formal genetics: from Gregor Mendel to Max Delbrück

Gregor Mendel's *Versuche über Pflanzen-Hybriden* (1866) is recognised as the foundation of what later became the science of genetics. Unlike most other fields of biology, genetics from its beginnings has been close to physics and mathematics. Mendel received an education not only in botany, but also in the physical sciences before he began his experiments on pea hybridisation. His aim to find a "generally applicable law" (governing the formation and development of hybrids) is more reminiscent of the hard sciences than of biology. Unlike contemporary plant breeders Mendel considered it critically important to obtain exact numerical data for each of the traits he looked at. Convinced that there was a numerical order in nature, he succeeded to find equations by which the distribution of pea hybrids' properties in subsequent generations can be adequately described statistically. According to Mendel, discrete and independent factors (later called genes) accounted for the inheritance of each trait of an organism.

His allowance of chance to play a decisive role in natural processes¹ and his assumption that inheritance is “discrete”, and not “blending”, with discrete factors underlying seemingly continuous phenomena, bear similarities to developments in physics in the late 19th century. Statistical mechanics, the application of statistics to the physical branches of classical mechanics and thermodynamics, was the first physical theory in which probabilistic concepts and the notion of chance played a fundamental role. In this theory, which was founded by Ludwig Boltzmann and, independently, J. Willard Gibbs, the laws of nature only apply to large populations, and predictions are possible not for the causes of isolated events but with a probability for the totality of events. This also held true for Mendel’s rules.²

For various reasons Mendel’s work was largely neglected for 35 years. The “rediscovery” of his rules in 1900 by Carl Correns, Hugo de Vries and Erich Tschermak-Seysenegg marks the beginning of classical, or formal, genetics, which focussed on the transmission of traits from parents to offspring. In 1906 in England William Bateson coined the term “genetics”. He developed major concepts and a large part of the early terminology of the emerging science. The term “gene” as the “genotypic” basis of a distinct “phenotypic” trait was introduced by the Danish researcher Wilhelm Johannsen in 1909. His notion of the gene had a far-reaching impact; while realising that the behaviour of genes had something in common with “chemical bodies”, he concluded nevertheless that this did not mean that genes themselves were chemical entities. He suggested that the term gene be used merely as an abstraction, “for the time being only

¹His frequent allusion to chance effects can be found, for example, in the following paragraph of his 1866 paper: “This represents the *average* result of the self-fertilization of the hybrids when two differentiating characters are united in them. ... It remains purely a matter of chance which of the two sorts of pollen may fertilize each separate egg cell”. Mendel’s paper, in its original German and in English translation, is available at www.mendelweb.org.

²For a comparison of Mendel’s approach with statistical mechanics see Francois Jacob, *The Logic of Life. A History of Heredity* (Princeton, 1993), pp.192–201.

something like a unit of calculation.”³ This gene concept became one of the most powerful abstractions in biology.

In 1910 Thomas Hunt Morgan in the United States observed a white-eyed mutant male among the red-eyed wild-type individuals of his new experimental object, *Drosophila*. Cross-breeding experiments showed that only males displayed this trait. Morgan concluded that it was sex-linked and its gene was carried on the X-chromosome. Experiments such as this one marked the beginning of a second phase of Mendelian genetics, in which Morgan and his collaborators, Alfred H. Sturtevant, Calvin B. Bridges and Hermann J. Muller, developed the chromosome theory of inheritance, according to which genes are located on chromosomes and transmitted in linkage groups unless crossover occurs. They succeeded to establish gene maps of the four chromosomes.⁴ By promoting the belief that the gene is the “basis of life” Muller emphasised the importance of the new science.⁵ He considered genes’ basic properties to be identical self-replication and heritable mutations, which he regarded as the basis of biological evolution.⁶ Already in 1922 he envisaged that geneticists would have to become bacteriologists, biochemists and physicists. But convinced that, at least at the time, “a gene cannot effectively be ground in a mortar or distilled in a retort”,⁷ he continued to pursue and propagate the indirect methods of formal genetics

³Wilhelm Johannsen, *Elemente der exakten Erblichkeitslehre* (Jena, 1909), pp. 124–125. The third edition (1926, p. 168) contains the same sentence. The literature on the history of genetics and molecular biology is numerous. Of the recent publications I mention Raphael Falk, “The gene — a concept in tension,” in: Peter Beurton, Raphael Falk, and Hans-Joerg Rheinberger, *The Concept of the Gene in Development and Evolution* (Cambridge, 2000), pp. 317–348. A classic in the history of early molecular biology, covering medical microbiology, virus research, biochemical and biophysical genetics is Robert Olby, *The Path to the Double Helix. The Discovery of DNA* (Seattle, 1974).

⁴Already in 1903 and 1904, respectively, Walter Sutton and Theodor Boveri, looking for a cytological basis of genetics, formulated early versions of the chromosome theory.

⁵Hermann J. Muller, “The gene as the basis of life”, *Proceedings of the International Congress of Plant Science*, 1929. Muller gave this speech in 1926.

⁶Hermann J. Muller, “Variation due to change in the individual gene”, *American Naturalist* **56** (1922), pp. 32–50.

⁷*Ibid.*

and, later, genetic radiation studies. His discovery in 1927 of artificial mutagenesis by X-rays opened up a new approach in genetics (see below) and also an important branch of environmental studies.

Morgan and his collaborators endowed genes with a location and some physical existence. But the search for the material nature of the gene was not relevant for this highly successful approach, as the following quotation from Morgan's Nobel lecture, as late as 1934, shows: "There is no consensus of opinion amongst geneticists as to what the genes are — whether they are real or purely fictitious — because at the level at which the genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle". As Max Delbrück later explained, in the mid-1930s genes were still "algebraic units of the combinatorial science of genetics, and it was anything but clear that these units were molecules analysable in terms of structural chemistry".⁸

Classical genetics soon became an exact biological discipline. The physicist Max Delbrück was fascinated with the fact that it was a logically self-contained autonomous exact science which was quantitative without using physical measures such as velocity and mass, in contrast to chemistry which had not obtained independence from physics.⁹

Muller's discovery that X-ray radiation causes mutations led to a collaboration of geneticists and physicists on the investigation of the biological effects of radiation. On Muller's suggestion, Berlin geneticist Nikolai Timoféeff-Ressovsky started collaborating with the physicist Karl G. Zimmer. They were joined by Max Delbrück in the early 1930s. As a theoretical physicist Delbrück was not experienced in experimental radiation research. In the following, I shall present some background information on his becoming a biologist and geneticist.

⁸Max Delbrück, "A physicist's renewed look at biology: Twenty years later", *Science* **168** (1970), pp. 1312–1315. According to Delbrück, genes "could have turned out to be submicroscopic steady-state systems, or they could have turned out to be something unanalysable in terms of chemistry, as first suggested by Bohr".

⁹Max Delbrück, "On the nature of gene mutations and gene structure," in Nikolai W. Timoféeff-Ressovsky, Karl G. Zimmer und Max Delbrück, "Über die Natur der Genmutation und der Genstruktur", *Nachrichten von der Gesellschaft der Wissenschaften zu Göttingen (Mathematisch-Physikalische Klasse)* **1** (1935), pp. 189–245.

Delbrück spent three post-doctoral years (1929–32) in England, Switzerland and Denmark. The encounter with a new language and culture in England and the association with Wolfgang Pauli in Switzerland and Niels Bohr in Denmark influenced him deeply. Bohr's speculation that the complementarity argument of quantum mechanics might be applied to the explanation of phenomena of life, summarised in his 1932 lecture "Light and life",¹⁰ aroused Delbrück's interest in biology. Bohr assumed that the laws of biology might be complementary to those of physics and chemistry in a similar way as the "spatial continuity of light propagation" according to electromagnetic theory is complementary to the "atomicity of the light effects", the light quanta. Both features are aspects of one reality, the phenomenon of light, and cannot contradict each other because a closer analysis of each aspect would demand "mutually exclusive experimental arrangements".¹¹ Bohr regarded the existence of life as an "elementary fact that cannot be explained, but must be taken as a starting point in biology" and concluded with the vitalistic notion that "the asserted impossibility of a physical or chemical explanation of the function peculiar to life" would be "analogous to the insufficiency of the mechanical analysis for the understanding of the stability of atoms".

Bohr's notion of biology stood in stark contrast to the view that Jacques Loeb, a German-American biologist and biochemist, had propagated forcefully from the late 19th century. Loeb asserted that life phenomena can be explained by chemical and physical methods, and that biologists had to use and develop these methods further if they wanted to work scientifically. Already in the 1910s Loeb stimulated the earliest experimental attempts to associate (but not equate) genes and enzymes. As it turned out a few years later, Bohr's hopes, that in biology completely different laws from those in physics might be found, were not fulfilled. Instead, Loeb's "mechanistic" programme culminated in Watson's and Crick's theory of the double helix structure of

¹⁰Bohr's lecture was published in *Nature* **131** (1933), pp. 421–423; 457–459.

¹¹Ibid. On the impact of Bohr's complementarity concept see for example Ernst P. Fischer and Carol Lipson, *Thinking about Science. Max Delbrück and the Origins of Molecular Biology*, New York, 1988.

DNA, in which “complementarity” became an entirely chemical concept: the specific pairing of DNA’s four bases, through weak forces of hydrogen bonds, according to their chemical structure.

In the 1930s, however, Bohr’s romantic views motivated Delbrück and a few other physicists to search for new laws of life. Back in Germany, where he became an assistant to Lise Meitner at the Kaiser Wilhelm Institute (KWI) for Chemistry in 1932, Delbrück founded a discussion group of biologists and physicists. It led to a co-operation with Timoféeff-Ressovsky and Zimmer and the publication of a lengthy and influential joint paper *Über die Natur der Genmutation und der Genstruktur*, which consisted of three separate contributions and a joint conclusion by its authors.¹²

A central point of the paper, often referred to as the “Three-Man-Work”, was the physical interpretation of the gene. Delbrück wrote a theoretical section entitled *Atomphysikalisches Modell der Genmutation*, which is acknowledged to be of fundamental importance in the history of molecular biology. Reflecting on the nature of the stability of the gene as a “well-defined association of atoms”, Delbrück was the first to develop the notion of genes as something similar to macromolecules. The problem of the two aspects of mutations, change and constancy of the change, was solved by assuming that the stability of the gene was caused by the strength of interatomic forces and its mutation by a quantum jump from one stable configuration to another through certain forms of energy from the outside. Notwithstanding the fact that Delbrück did not expect chemistry to provide the solution for the question of the nature of the gene — for example, he did not relate its stability to a molecular configuration — he presented for the first time a theoretical concept that made genes approachable by physical and chemical means.

His elaboration had strong direct and indirect effects. Impressed with Delbrück’s thoughts, Warren Weaver from the Rockefeller Foundation in 1936 offered him a fellowship for a stay in the United States. In 1938 Delbrück’s paper motivated the physiologist Salvador Luria, a Jewish refugee from Italy in the United States, to take pains to start collaboration with Max Delbrück. Finally, in 1944, Delbrück’s

¹²Timoféeff *et al.*, “Über die Natur”.

paper became the central constituent of Erwin Schrödinger's book, *What is Life*.

Unlike other physicists, Delbrück did not continue to deal with radiation experiments in order to understand the nature of genes. As he stated with hindsight, his decision was a right one: the hope "to get at the chemical nature of the gene by means of radiation genetics never materialised. The road to success effectively bypassed radiation genetics".¹³ In particular, the application of the "target theory", a theoretical stochastic model of radiation-induced effects, to mutation analysis did not prove fruitful for elucidating properties of the gene, such as its size. Instead, Delbrück was fascinated with the discovery of the American biochemist Wendell Stanley in 1935 that a certain virus, the tobacco mosaic virus (TMV), could be crystallised. Since viruses are able to replicate identically Delbrück concluded that TMV could be used as a primitive model of the gene, and that virus research might be relevant "for a general assessment of the phenomena peculiar to life".¹⁴ Interestingly, already in 1937 he sensed that these phenomena might be simpler than anticipated by Bohr: "One should view replication not as complementary to atomic physics but as a particular trick of organic chemistry".¹⁵

After 1933, Delbrück was not dismissed from his position at the KWI. However, due to his "misbehaviour" at a Nazi training course for university teachers, he was not immediately accepted for *Habilitation*. Instead of staying in Berlin and trying again to pursue an academic career, he accepted a fellowship provided by the Rockefeller Foundation and in 1937 moved to the United States. After visiting various laboratories he became convinced that neither *Drosophila* nor TMV were experimental objects suited for studying gene replication. Only when he found a congenial experimental object, phage (bacterial viruses), with which he was able to achieve fast and clear cut quantitative results on phage growth and mutation, did he become a biologist.

Genetic research in phage, as it was initiated by Delbrück, who was soon followed by Salvador Luria and Alfred Hershey, proved successful in tackling problems such as gene mutation and replication. An

¹³Delbrück, "A physicist's renewed view".

¹⁴Ibid., appendix 1 (Delbrück's notes of 1937).

¹⁵Ibid.

example is the so-called fluctuation experiment.¹⁶ Luria and Delbrück showed quantitatively that adaptation of bacteria to virus resistance was a result of random mutations occurring prior to contact with the virus and subsequent selection and not, as was widely believed, of directed mutations in a Lamarckian sense. Elie Wollman, a molecular biologist at the Institut Pasteur in Paris, later characterised the novelty of the approach of the phage group as compared with that of earlier researchers on phage:

“Taking a strictly Cartesian attitude, Delbrück and Luria had swept away the facts and interpretations accumulated by their predecessors over twenty years and started anew. Within a few years they, and the small group of other workers they had attracted by the simplicity, the precision, and the elegance of their new departure, had made tremendous advances”.¹⁷

Phage genetics thrived in the United States and, after the second world war, was imported into Europe, where it developed rapidly at the Institut Pasteur in Paris. For various reasons it took longer until it became established in Germany.¹⁸ Carsten Bresch, a pioneer of this research in Germany, presents details of its beginnings in his contribution in this volume.

Unlike phage genetics, biochemical and genetic TMV research were imported from the United States in 1937 by Adolf Butenandt, Alfred Kühn and Fritz von Wettstein and established at the Division for Virus Research at the KWIs for Biology and Biochemistry. After the second world war, TMV research was conducted at the MPI for Virus Research, but universities did not take it up. According to botanist and TMV researcher Georg Melchers this was due, among other things, to the “lack of insight into the general importance of a field

¹⁶Salvador Luria and Max Delbrück, “Mutations of bacteria from virus sensitivity to virus resistance”, *Genetics* **28** (1943), pp. 491–511.

¹⁷Elie Wollman, “Bacterial conjugation”, in John Cairns, Gunther S. Stent and James D. Watson (eds.), *Phage and the Origins of Molecular Biology* (New York 1966), p. 216.

¹⁸For details see U. Deichmann, “Emigration, isolation and the slow start of molecular biology in Germany”, *Studies in the History and Philosophy of Biological and Biomedical Sciences* **33** (2002), pp. 433–455.

that was dealing with such a specialised object as the pathogenic agent of a single plant disease" among university professors.¹⁹ In addition, the requirement of a large amount of land and time made the carrying out of TMV research at universities difficult. See also the contribution by Karl-Wolfgang Mundry in this volume.

Phage research, by contrast, had few requirements and gave fast results. Wolfhard Weidel, an early phage and bacteria geneticist at the KWI (MPI) for Biology, explained the general importance of phage research by the fact that it is not "self-contained as may be the case with the systematics of leafhoppers", but "aimed at the solution of biological and biochemical problems of the most general and most far-reaching implications, namely: mode of codification of genetic information in nucleic acid molecules, mechanism of realization of genetic information carried by such polynucleotide chains; mechanism of their exact replication; and, finally, mechanism of mutation and genetic recombination at the molecular level".²⁰

The chemists' conservative breakthroughs in genetics: from Friedrich Miescher to Oswald T. Avery

DNA as a phosphorus-containing substance with a high molecular weight was discovered in 1869 by the Swiss biochemist Friedrich Miescher at the University of Tübingen. The "nuclein" which he isolated from nuclei of lymphocytes, consisted — as chemists showed shortly afterwards — predominantly of DNA and some percentage of protein.

For many years the chemical analysis of DNA did not provide any evidence that it possessed the diversity required for the carrier of hereditary information. The assumption formulated in 1906 that DNA

¹⁹Georg Melchers, "Warum interessiert den Biologen das Tabakmosaikvirus", *Jahrbuch der MPG* (1960), pp. 90–113 (translation by UD). TMV research has been reviewed by Angela N.H. Creager (*The Life of a Virus. Tobacco Mosaic Virus as an Experimental Model, 1930–1965*, Chicago, 2002); concerning Germany see also Christina Brandt, *Metapher und Experiment. Von der Virusforschung zum genetischen Code*, Göttingen, 2004.

²⁰Wolfhard Weidel, "Bacterial viruses (with particular reference to adsorption/penetration)", *Annual Review of Microbiology* **12** (1958), p. 27.

is a small uniform molecule made up of four nucleotides (the tetranucleotide hypothesis) became generally accepted. When the macromolecular nature of DNA was demonstrated in the late 1930s, DNA was thought to be a repetitive polymer comprised of repeating units of tetranucleotides. This hypothesis was critically examined only after Avery's 1944 discovery of DNA's crucial role in bringing about lasting transformations in bacteria (see below).

It should be mentioned that in the 1930s proteins, too, were believed to show regularities in their structures. But due to the large variety of proteins in the cell and the increasing evidence that enzymes and antibodies consist entirely or largely of proteins, the assumption that only proteins are the carriers of biological specificity — that is, the substances responsible for bringing about specific properties of species or individuals and specific biochemical reactions in cells — became almost universally accepted.

When scientists began to experimentally examine the question of the physical and chemical nature of genes in the 1930s, first by radiation studies, and then by virus research, their consensus was that genes, too, must be proteins. The already mentioned crystallization of TMV by Wendell Stanley in 1935 supported this view, because he wrongly identified it as a pure protein. When Norman Pirie and Frederick Bawden showed shortly after that TMV also contained RNA, genes were thought to be nucleoproteins; the specificity lying in the protein part of the molecule.

In the late 1930s a number of different experiments showed the crucial importance of DNA for cell replication and mutation.²¹ In 1936 the Swedish biologist Torbjörn Caspersson demonstrated, by UV absorption, that DNA replication took place at the onset of cell division. Several research groups between 1939 and 1941 showed that the UV-mutation spectrum was identical with the DNA absorption spectrum. However, researchers concluded that DNA had only an auxiliary function. The hypothesis that DNA is the material of genes, obvious as it may sound in hindsight, fell victim to the dogma that genes must be proteins. When Erwin Schrödinger, in his well-known book, *What is Life* (1944),

²¹Robert Olby, *The Path to the Double Helix. The Discovery of DNA* (Seattle, 1974), pp. 105–107.

speculated on how genetic information might be stored linearly in genes, he too, took it for granted that genes were proteins.

Oswald Theodore Avery was an outstanding microbiologist and immunochemist at the Rockefeller Institute for Medical Research. In 1944, Avery and his younger associates, Colin MacLeod and Maclyn McCarthy, demonstrated that the substance capable of bringing about a lasting transformation of pneumococcal types — that is, apparently heritable changes — was DNA. This was the first time that a genetic phenomenon was clearly associated to a nucleic acid. It challenged the then generally accepted view that proteins were the material of genes. Their discovery thereby became the basis of all further studies on the structure and genetic functions of DNA.

Avery's paper also had strong methodical impacts. It showed that the physical nature of genes can be analysed *directly* — in contrast to the highly favoured indirect methods of radiation and virus (including phage) research — and it called for chemistry, in particular the chemistry of DNA, to be added as a tool to analyse the gene. As microbiologist Bernard Davis perceived it, “the Avery discovery was truly revolutionary” because of its intrinsic significance and unexpectedness.²²

Avery's paper was received with open, but restrained, appreciation. However, it was neglected particularly by the phage group around Max Delbrück. As Avery's collaborator René Dubos explained, “certain members of the ‘phage group’ regarded the orthodox chemical approach to the understanding of biological phenomena as pedestrian, too slow, and not revolutionary enough for their intellectual ambition, ... they did not seem able to do much with or build on [Avery's experiment]”.²³ Only when two members of this group, Alfred Hershey and Martha Chase, in 1952 demonstrated the importance of DNA for phage replication, did Avery's conclusion become acceptable to them.

Stimulated by Avery's results, the biochemists Rollin Hotchkiss and Erwin Chargaff in the late 1940s were the first to conduct a quantitative

²²Bernard Davis, *BioEssays* 9 (1988), pp. 130–131. Details on the impact and reception of Avery's 1944 experiment are in Ute Deichmann, “Early responses to Avery's *et al.*'s 1944 paper on DNA as hereditary material”, *Historical Studies in the Physical and Biological Sciences* 34(2) (2004), pp. 207–233.

²³Dubos, *The Professor*, p.158.

base analysis of DNA by paper chromatography. Chargaff speculated in 1947 that, among other things, differences in the proportions or in the sequence of the nucleotides forming the nucleotide acid chain could be responsible for specific biological effects. This far reaching hypothesis anticipated linear genetic coding. Two years later he and his collaborators demonstrated that DNA is not a repetitive molecule, but that the DNAs of different species are chemically different. This work led to the discovery of the so-called Chargaff rules of base ratios in DNA (A/T and G/C equal one), first stated in 1950, and which in 1953 found its explanation in the specific base-pairing postulated in Watson's and Crick's double helix theory of DNA structure.

Through their work in X-ray crystallography, physicists and physical chemists had maintained a strong impact on the further development of genetics at the molecular level. Convinced that Avery had shown that genes were made of DNA and not proteins, Maurice Wilkins started X-ray studies on DNA.²⁴ At a scientific meeting in Naples in the spring of 1951 Wilkins alerted James Watson to X-ray work on DNA. Watson, in turn, motivated Francis Crick in Cambridge, who conducted X-ray studies on proteins for his dissertation, to shift his interest from proteins to DNA.

Outlook — the double helix, the genetic code and biochemistry

The history of the elucidation of the double helix structure of DNA by Watson and Crick in 1953 has been much written about, including by the two scientists themselves. Their work brings together different pathways of, and approaches to, research in genetics. Crick was a physicist who had left physics in order to study the structure of proteins with Max Perutz. Watson was a biologist who, motivated among other things by Schrödinger's book, *What is Life*, had joined the phage group and completed his dissertation under Luria. Watson's

²⁴Maurice Wilkins, "DNA at King's College, London", in Donald Chambers (ed.), *DNA: The Double Helix*, Annals of The New York Academy of Sciences, 1995, pp. 200–204.

and Crick's work encompasses X-ray crystallography by Rosalind Franklin and Wilkins, Chargaff's chemical analysis of DNA, and Linus Pauling's theories of the nature of the chemical bond and the role of weak forces such as hydrogen bonds in the structure of macromolecules. They also used Pauling's method of model building.

Max Delbrück pointed to the extraordinary scientific importance of the discovery by comparing it to the discovery of the basic structure of atoms by Ernest Rutherford in his famous gold foil experiment: "Very remarkable things are happening in biology. I think that Jim Watson has made a discovery which may rival that of Rutherford in 1911".²⁵

Watson's and Crick's elucidation of the DNA double helix structure opened up another phase of molecular genetics, in which the focus was on gene replication and the genetic code. In their seminal 1953 paper, they made it very clear that they perceived a possible implication of the proposed DNA structure for replication: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material".²⁶ It took four years until the semi-conservative replication mechanism had been solved in principle by Matthew Meselson and Franklin Stahl.

In contrast, the problem of the genetic code was much more complicated. Watson and Crick were the first to use the term "information" for what had been called "biological specificity" before: "The phosphate-sugar backbone of our model is completely regular, but any sequence of the pairs of bases can fit into the structure. It follows that in a long molecule many different permutations are possible and it therefore seems likely that the precise sequence of the bases is the code which carries the genetic information".²⁷

In 1948 Shannon had introduced information theory into mathematics. Biologists used the term information increasingly, but usually

²⁵Max Delbrück to Niels Bohr, 14 April, 1953, Delbrück papers, Caltech Archives.

²⁶James D. Watson and Francis H. C. Crick, "A structure for deoxyribose nucleic acid", *Nature* 171 (1953), pp. 737–738.

²⁷James Watson and Francis Crick, "Genetical implications of the structure of deoxyribonucleic acid", *Nature* 171 (1953), pp. 964–967.

only as a metaphor.²⁸ Physicists were immediately attracted by the coding problem of DNA. Already in 1954, the astronomer George Gamow, a consultant in the United States Navy during the cold war (thus being well acquainted with coding problems) and, incidentally, a friend of Max Delbrück's, presented an exact phrasing of the coding problem and developed the concept of heredity as information transfer: "The hereditary properties are characterized by a long number written in a four digital system, proteins can be considered as long 'words' based on a 20-letter alphabet. The question arises about the way in which four digital numbers can be translated into such 'words'".²⁹ Coding was defined as — and largely remained for about seven years — an abstract physical problem independent of biochemical considerations.

Various overlapping triplet codes were theoretically developed by Gamow, Richard Feynman, Edward Teller and other physicists. The arguments for an overlapping code were partly taken from engineering: there would be a better matching of dimensions between protein and DNA-template; storage density would be maximised and waste of information capacity avoided.³⁰ However, these arguments did not withstand experimental testing. In 1957, Sydney Brenner and Crick ruled out, experimentally and by logical reasoning, an overlapping code. Using frameshift mutations, in which base-analogues (e.g. acridines) were inserted into DNA, they demonstrated for the first time that the code was, as had been predicted, a triplet code. Only three mutations of the same type led to (partially) functioning proteins. Brenner invented the word "codon" to describe the nucleotide unit that would specify an amino acid.

During the next years Leslie Orgel, Carl Woese, Crick and others designed various purely theoretical non-overlapping comma-free codes, which would make sense only if read in one frame. On the

²⁸Lily Kay, *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford 2000).

²⁹George Gamow, "Possible relation between deoxyribonucleic acid and protein structures", *Nature* **173** (1954), p. 318.

³⁰Brian Hayes, "The invention of the genetic code", *American Scientist* **86** (1998), pp. 8–14.

assumption of a one-to-one relationship between the number of codons and the number of amino acids, Crick's elegant code coded for just 20 amino acids (among others, the codons AAA, GGG, CCC and UUU were ruled out because, if combined with themselves, they would cause reading-frame ambiguity). Woese later wrote about the fascination with these codes:

"The comma-free codes received immediate and almost universal acceptance. ... They became the focus of the coding field, simply because of their intellectual elegance and the appeal of their numerology. ... For a period of five years most of the thinking in this area either derived from the comma-free codes or was judged on the basis of compatibility with them."³¹

In 1961 two outsiders of the field experimentally refuted Crick's elegant proposal and deciphered the first "code word". Heinrich Matthaei and Marshall Nirenberg showed that artificial RNA can stimulate protein synthesis in a cell-free system: poly-Uracil RNA coded for poly-phenylalanine, the codon for this amino-acid thus being UUU. Their work opened up a next, largely biochemical phase in the history of the genetic code, in which the codons for all amino acids were deciphered in about six years. In the end, the code did not resemble most of the theoretical notions: the magic number of 20 does not play a role; all the mathematical solutions to solve the frame-shift problems are not used; and the code is redundant (many amino acids have several codons each).

Is it thus fair to say that physicists were mainly wrong and biochemists mainly right? Such a simplistic assessment completely neglects the decisive role of theory. As Carl Woese later observed, "What has not generally been appreciated is that the subsequent spectacular advances occurring in the second period [1961–67] were interpreted and assimilated with ease, their values appreciated, and new experiments readily designed precisely because of the conceptual framework that had already been laid".³²

³¹Cited after Hayes, *ibid.*

³²Kay, *Who Wrote the Book*, p. 129.

Partly parallel to the developments discussed here, decisive contributions were made to the elucidation of protein biosynthesis (see also the contribution by Hans Zachau in this volume) and gene regulation. For reasons of brevity, they are not discussed here. The articles collected in a recent volume highlight the importance of biochemistry in studies on protein biosynthesis.³³

In a paper titled “Biochemistry strikes back”, Sydney Brenner recalls the changing relationship between theoretical approaches and (biochemical) experiments in molecular biology: “The early days of molecular biology were marked by what seemed to many to be an arrogant cleavage of the new science from biochemistry”.³⁴ But molecular biology, according to Brenner “a way of life and not a subject”, effected a fusion between biochemistry and genetics. He holds the conviction that despite the recent increase and success of “omic science” — genomics, transcriptomics, proteomics — problems such as protein interactions will not be solved by proteomics. Biochemistry will flourish in the future, too, “because it provides the only experimental basis for causal understanding of biological mechanisms.”³⁵ Jacques Loeb’s programme still appears to be alive. Many contributions to this volume bear witness to it.

³³Jan Witkowski (ed.), *The Inside Story. DNA to RNA to Protein* (New York 2005).

³⁴Sydney Brenner “Biochemistry strikes back”, in Jan Witkowski (ed.), *The Inside Story*, pp. 367–369.

³⁵Ibid.