Forty years under the central dogma

The Central Dogma. This states that once 'information' has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the precise determination of sequence, either of bases in the nucleic acid or of amino-acid residues in the protein[1].

The quotation above is from a seminal paper, 'On Protein Synthesis,' presented by Francis Crick at the 1957 annual meeting of the Society of Experimental Biology and published in 1958[1]. In this paper, Crick listed the standard set of 20 amino acid residues for the first time; argued that 'the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein'; argued that the three-dimensional conformation of a protein must be determined by its amino acid sequence; pointed out that protein synthesis must be sequential; and presented his hypothesis of 'adaptor' molecules mediating protein formation at the ribosome. Most importantly, Crick formulated what he called the 'Central Dogma', which is the focus of this article.

The Central Dogma had and still has an influential place in molecular biology. It has been a constant point of reference that served as a distinctive icon for proponents of the new molecular biology of the late 1950s and 1960s. However, it has also provided a target for many criticisms of the molecular approach. In this article, we give a short overview of the history of the Central Dogma, in the hope of stimulating further reflection and analysis.

Introduction of the concept of information into biology

The concept of information, introduced into molecular biology only five years earlier, stands at the core of Crick's view of protein synthesis. In 1953, Ephrussi, Leopold, Watson and Weigle[2] suggested that the term 'interbacterial information' be introduced in order to allow navigation through what they perceived as a terminological morass into which bacterial genetics had entered. The objects of concern were terms such as transformation and transduction, which had come into vogue during the preceding decade. This was the first printed use of the word information in what became molecular biology. Although, Ephrussi *et al.*[2] did not define the term, its use spread almost immediately. In 1956, Mazia[3] argued that the role of RNA was to carry information from nuclear DNA to the cytoplasm, for protein synthesis. Spiegelman argued that only RNA and DNA had sufficient informational complexity to serve as templates for protein formation[4], and Lederberg noted perceptively that 'information' was what 'specificity' was 'called nowadays'[5]. It remained for Crick, in 1958, to incorporate Lederberg's observation into an explicit definition of information as the 'specification' of sequence[1].

Crick's scheme for protein synthesis puts DNA at the centre of attention. According to this scheme, DNA or, more generally, nucleic acids are the source of a unidirectional information flow ultimately specifying proteins. This linear scheme contrasts with former circular schemes for protein synthesis, where proteins specify proteins ad infinitum[6]. Earlier in the 1950s, some biologists had already proposed a way out of the circle by positing a role for nucleic acids as templates for protein synthesis[7]. In this context, Crick's move capped the development of a gene-centred view of biological processes that had been gradually emerging since the 1920s.

Interpretations of the Central Dogma

The most obvious interpretation of Crick's original (1958) formulation of the Central Dogma is in negative terms. The Central Dogma only forbids a few types of information transfer, namely, from proteins to proteins and from proteins to nucleic acids. However, after its rapid adoption by most of the biologists interested in protein synthesis, it was most often interpreted or reformulated in a more restrictive way, constricting the flow of information from DNA to RNA and from RNA to protein (Fig. 1)[8].

According to Watson's autobiography, he had already derived this 'formula' (Fig. 1) in 1952[9]. In fact, such schemes were commonly entertained during the early 1950s, at least among the biologists interested in protein synthesis. This is attested to, for example, by a figure published by Jean Brachet[10] in 1952, and by the English summary of a paper published in French by Boivin and Vendrely[11] in *Experientia* in 1947. Much more restrictive than Crick's original statement, Watson's formula was immediately confronted with a series of possible exceptions, some of which are mentioned below. Crick, meanwhile, remained rather cautious in his interpretation of the Central Dogma. On several occasions, he felt it necessary to come back to his original idea and explicate what he thought to be its correct interpretation. For example, in 1970, Crick[12] devoted a paper specifically to the Central Dogma, including a diagram reportedly conceived (but not published) in 1958.

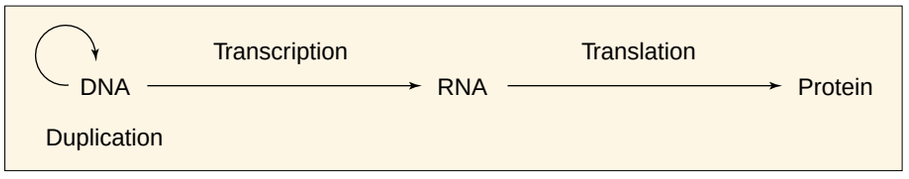

Figure 1

The Central Dogma as envisioned by Watson in 1965. 'We should first look at the evidence that DNA itself is not the direct template that orders amino acid sequences. Instead, the genetic information of DNA is transferred to another class of molecules, which then serve as the protein templates. These intermediate templates are molecules of ribonucleic acid (RNA)…Their relation to DNA and protein is usually summarised by the formula (often called the central dogma). [T]he arrows indicate the direction of transfer of the genetic information. The arrow encircling DNA signifies that it is the template for its self-replication; the arrow between DNA and RNA indicates that all cellular RNA molecules are made on DNA templates. Correspondingly, all protein sequences are determined by RNA templates. Most importantly, both these latter arrows are unidirectional, that is, RNA sequences are never copied on protein templates; likewise, RNA never acts as a template for DNA'[8]. Figure reproduced, with permission, from Ref. 8.

 0968–0004/98/$19.00 PII: S0968-0004(98)01244-4

In Crick's diagram (Fig. 2), the looped arrows represent the self-template properties of DNA and RNA, whereas the other solid arrows represent the same unidirectional flow of information that was represented in Watson's 1965 formula. Crick also explicitly mentions the possibility of a direct flow of information from DNA to proteins, as well as of a reverse flow of information from RNA to DNA. As in the original 1958 formulation, the only information flows that are forbidden are those from protein to DNA or RNA, and from protein to protein. Crick wrote the following.

> *The discovery of just one type of present-day cell which could carry out any of the three unknown transfers would shake the whole intellectual basis of molecular biology, and it is for this reason that the Central Dogma is as important today as when it was first proposed*[12].

According to Crick, three types of transfer could be distinguished on the basis of the available data: 'unlikely' transfers from proteins to nucleic acids; 'possible' transfers from RNA to DNA and from DNA to proteins; and finally 'known' transfers (e.g. from DNA to RNA to proteins, plus auto-transfers involving DNA or RNA). Strikingly, Crick emphasized auto-transfers involving RNA, over RNA to DNA transfers. Although it was clear by 1958 that some viruses used RNA as a carrier of genetic information, clear indications of the existence of RNA duplication had to wait until the early 1960s.

It is necessary to consider Crick's remarks in the light of his own conception of the respective roles of theory and experiment. In his view, the role of theory is primarily heuristic. In 1958, Crick prefaced the formulation of both the Sequence Hypothesis and the Central Dogma with the following paragraph.

> *My own thinking (and that of my colleagues) is based on two general principles, which I shall call the Sequence Hypothesis and the Central Dogma. The direct evidence for both of them is negligible, but I have found them to be of great help in getting to grips with these very complex problems. I present them here in the hope that others can make similar use of them. Their speculative nature is emphasised by their names. It is an instructive exercise to attempt to build a useful theory without using them. One generally ends in the wilderness*[1].

Similar arguments can been found in other papers by Crick – for instance, in his 1963 review of the 'coding problem'[13]. In an interview with H. F. Judson in 1975, Crick emphasized the original speculative dimension of the Central Dogma.

> *My mind was, that a dogma was an idea for which there was no reasonable evidence…I just didn't know what dogma meant. And I could just as well have called it the Central Hypothesis…Dogma was just a catch phrase. And of course one has paid for this terribly, because people have resented the use of the term dogma, you see, and if it had been Central Hypothesis nobody would have turned a hair*[14].

The Central Dogma's impact in the early 1960s

Even a rudimentary citation analysis of Crick's 1958 paper gives some insight into its influence. In the early 1960s, the paper was quite widely cited but never reached levels as high as, for example, Watson and Crick's 1953 DNA-double-helix paper[15], or Jacob and Monod's 1961 operon paper[16] – both of which had hundreds of citations per year for more than a decade. However, a closer look at the citations of Crick's paper reveals that several established biologists, and almost all of the rising stars of the new biology, cited the 1958 paper on at least one occasion (e.g. G. W. Beadle, S. Benzer, S. Brenner, J. N. Davidson, M. B. Hoagland, F. Jacob, S. E. Luria, J. Monod, S. Ochoa, G. Pontecorvo, M. F. Singer, F. Vogel, J. D. Watson, C. Yanofsky, M. Ycas and G.E. Zubay, among many others).

The extent of this influence can be attributed to the fact that the Central Dogma, together with the notion of base-pair complementarity in DNA, provided a theoretical framework for molecular biologists interested in protein synthesis and mechanisms of gene expression. Consequently, the main focus of much of that research shifted from proteins to DNA. Even though most cellular functions were still thought to be carried out by proteins (enzymes), the central problem addressed by the new molecular biologists became that of understanding how hereditary information encoded in DNA is translated into specific enzymatic configurations. A thorough answer to this question, however, had to await the characterization of the different molecules involved in the processing of genetic information (messenger and transfer RNAs, and RNA polymerases). In short, the establishment of the molecular mechanisms that account for the information processing envisioned by Crick proved to be much more complex than expected and required the contributions of various independent lines of research[17].

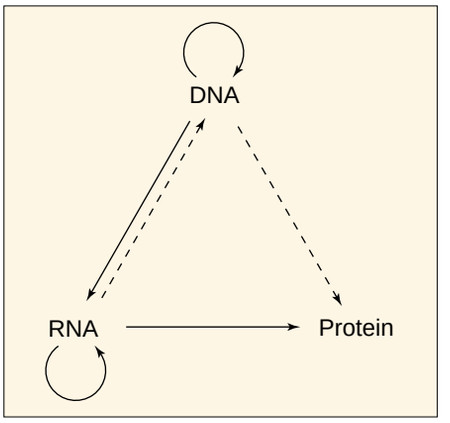

Figure 2
The situation envisioned in 1958. Crick described the figure using the following words. 'The arrows show the situation as it appeared in 1958. Solid arrows represent probable transfers, dotted arrows possible transfers. The absent arrows represent the impossible transfers postulated by the central dogma. They are the three possible arrows starting from proteins'[12]. Figure reproduced, with permission, from Ref. 12.

During the 1960s, the efforts of bacterial geneticists, biophysicists and biochemists led progressively to a comprehensive molecular picture of protein synthesis. The emerging community of molecular biologists succeeded in spreading their concept of gene expression in informational terms – that is, in terms of information transfer, transcription and translation. The Central Dogma was easily stated, explained and taught, and offered a clear landmark by comparison with the complex and sometimes confusing picture of the 1950s. Watson's 1965 textbook[8] and its successive editions were critically influential in the spread of the informational molecular gospel.

Challenges to the Central Dogma

From the time of its first formulation, however, experimental results threatened the Central Dogma, at least in the case of its most restrictive definitions (e.g. Watson's definition). In the 1950s, several groups working on the tobacco mosaic virus (TMV) questioned DNA's monopoly in carrying hereditary specifications. In 1956, a series of experimental results were converging towards RNA as the genetic material in TMV[18–20]. Thus, it was possible to bypass DNA and, there-

fore, the first step of Watson's scheme. RNA viruses, as they are now called, provided still more surprises. In 1970, two groups independently reported the characterization of an RNA-dependent DNA polymerase isolated from Rous sarcoma viruses[21,22]. Confirming earlier suspicions, these results clearly demonstrated the possibility of a flow of information from RNA to DNA. These findings prompted Crick[12] to write his 1970 piece for *Nature*, in which he explicitly showed how the new facts fitted into his scheme.

Bolder criticism of the general relevance of the Central Dogma was also made. For example, Barry Commoner[23,24] published several papers directly questioning the exclusive role of nucleic acids in inheritance. Relying on several sets of experimental results that indicated that compounds other than DNA (e.g. DNA polymerase and aminoacyl-tRNA synthetase) affect the result of transcription, Commoner replaced the unidirectional flow of information prescribed by the Central Dogma with a more complex scheme that explicitly includes feedback from proteins to DNA and RNA (Fig. 3). Though widely disseminated, Commoner's point of view found little support, even among those responsible for the observations on which the scheme was based.

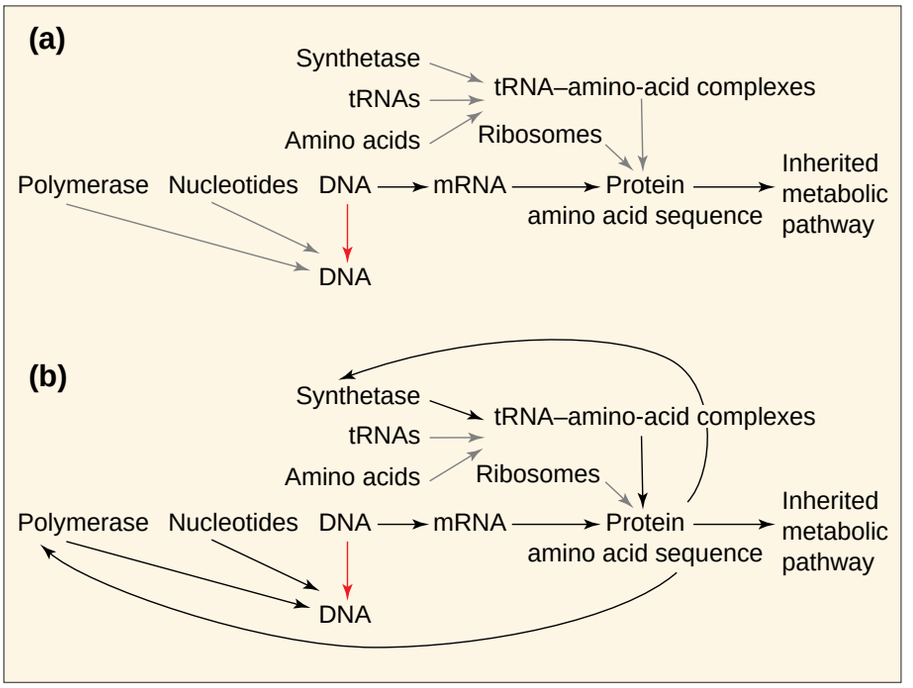

Figure 3

(a) Transfer of biochemical specificity in the system proposed by the theory of the DNA code[23]. **(b)** Modification accounting for the evidence that part of the biochemical specificity of DNA originates in the polymerase enzyme that catalyses DNA synthesis, and possibly in the relative availability of the several requisite nucleotides. Also shown is the effect of the contribution of specificity originating in amino-acid-tRNA synthetase, an enzyme that is essential to protein synthesis. Grey arrows indicate that one process is essential for the other, but does not determine the latter's specificity; black arrows indicate that one process determines another's specificity and is a regulatory component; red arrows indicate self-duplication. Figure adapted, with permission, from Ref. 23.

During the 1970s, molecular biologists began to work on eukaryotes (rather than almost exclusively on prokaryotic systems). A number of surprises resulted. One of the most striking was the recognition (from 1977 onwards) of the widespread occurrence of non-coding sequences in genes, which led to the distinction between introns and exons being made, and to the discovery of splicing mechanisms[25,26]. Moreover, alternative or differential splicing (i.e. the production of different mature mRNAs from the same transcript) was discovered[27], and a regulatory role for splicing was suggested by Gilbert[28] in 1978. With respect to the Central Dogma, this discovery has at least two limiting consequences: (1) the specification of protein sequences must thus be considered as discontinuously encoded in DNA; and (2) additional feedback from regulatory proteins is needed to ensure proper RNA splicing. Together, these two facts preclude the possibility of inferring the protein sequence solely from the DNA sequence, an idea that was a key consequence of Crick's Central Dogma and the Sequence Hypothesis.

At the end of the 1980s, several types of mRNA editing were reported, first in the genomes of the mitochondria of some unicellular eukaryotes (paramecia, trypanosomes), but soon also in some metazoan cell types[29]. These editing processes include deamination of cytosine to yield uracil, in mRNA, and the reverse process. Even more unusual behaviours have been observed involving mitochondrial RNAs in which bases can be deleted or inserted. This led to observations interpreted as indicating the formation of proteins for which there are not genes. In an extreme case, in the human parasite *Trypanosoma brucei*, as many as 551 uracils are inserted throughout the transcript that codes for NADH dehydrogenase subunit 7, and 88 are deleted[30]. When looking at the DNA segment that encodes a primary transcript, it is impossible to predict the sequence of amino acid residues in the final protein with complete certainty.

Still another challenge is provided by an infectious neurological disease first found in sheep and called scrapie. As early as the 1960s, the scrapie agent was shown to behave rather strangely. Smaller than all known viruses, it resisted various stringent treatments known to destroy nucleic acids or to inactivate most proteins. As repeated attempts to characterize any nucleic acid associated with this disease failed, several unorthodox explanations were proposed. At first not taken seriously by most researchers, the most controversial of them involved a protein-only agent, christened the prion, which was proposed to either induce the expression of a normally silent host gene or catalyse post-translational changes in a normal cell protein[31]. This hypothesis soon received support when a host gene coding for a protein that matches the sequence of the pathogenic agent was isolated. Today, debates on the very nature and mechanisms of prion transmission and expression still go on, but most researchers now accept the idea of a protein-only infectious agent. Clearly, this idea implies the occurrence of a protein–protein transfer of some kind of specificity[32].

Finally, perhaps the most controversial challenge to the Central Dogma is provided by recent evidence for epigenetic inheritance in a wide variety of eukaryotic species[33]. Reportedly, part of the inherited specifications – what normally counts as information – are not encoded in the DNA sequence but, rather, are specified by other mechanisms, such as patterns of methylation

Box 1. Selected sources for the history of molecular biology

Books

Brock, T. D. (1990) *The Emergence of Bacterial Genetics*, Cold Spring Harbor Laboratory Press
Debru, C. (1987) *Philosophie Moléculaire. Monod, Wyman, Changeux*, Vrin
Jablonka, E. and Lamb, M. J. (1995) *Epigenetic Inheritance and Evolution: The Lamarckian Dimension*, Oxford University Press
Kay, L. E. *Who Wrote the Book of Life? A History of the Genetic Code*, Stanford University Press (in press)
Keller, E. F. (1995) *Refiguring Life: Metaphors of Twentieth Century Biology*, Columbia University Press
Judson, H. F. (1979) *The Eighth Day of Creation*, Simon & Schuster (Expanded edition: Cold Spring Laboratory Press, 1996)
Latour, B. and Woolgar, S. (1979) *Laboratory Life*, SAGE Publications
Morange, M. (1994) *Histoire de la Biologie Moléculaire*, La Découverte (English edition: *The History of Molecular Biology*, Harvard University Press, 1998)
Olby, R. (1974) *The Path to the Double Helix*, Macmillan Press (New edition: Dover Publications, 1994)
Portugal, F. H. and Cohen, J. S. (1977) *A Century of DNA*, MIT Press
Rheinberger, H-J. (1997) *Toward a History of Epistemic Things. Synthesizing Proteins in the Test Tube*, Stanford University Press
Sapp, J. (1987) *Beyond the Gene. Cytoplasmic Inheritence and the Struggle for Authority in Genetics*, Oxford University Press
Stent, G. (1971) *Molecular Genetics. An Introductory Narrative*, Freeman

Collections of essays

Burian, R. M. and Thieffry, D., eds (1997) *Research Programs of the 'Rouge-Cloître group'*. Special issue of *Hist. Philos. Life Sci.* 19, 1–144
Cairns, J., Stent, G. S. and Watson, J. D., eds (1966) *Phage and the Origins of Molecular Genetics*, Cold Spring Harbor Laboratory Press
De Chadarevian, S. and Gaudilliere, J. P., eds (1996) *The Tools of the Discipline: Biochemists and Molecular Biologists*. Special issue of *J. Hist. Biol.* 29, 327–462
Lwoff, A. and Ullman, A., eds (1979*) Origins of Molecular Biology. A Tribute to Jacques Monod*, Academic Press
Monod, J. and Borek, E., eds (1971) *Of Microbes and Life*, Cornell University Press
Rich, A. and Davidson, N. (1968) *Structural Chemistry and Molecular Biology*, Freeman
Sarkar, S., ed. (1996) *The Philosophy and History of Molecular Biology: New Perspectives*, Kluwer Academic Publishers
Soederqvist, T., ed. (1997) *The Historiography of Contemporary Science and Technology*, Harwood Academic Publishers

Other historical papers

Abir-Am, P. (1992) *Osiris* 7, 164–191
Burian, R. M. (1993) *J. Hist. Biol.* 26, 387–407
Creager, A. N. H. and Gaudillière, J-P. (1996) *Hist. Stud. Phys. Biol. Sci.* 27, 1–89
Darden, L. (1995) in *Concepts, Theories, and Rationality in the Biological Sciences* (Wolters, G. and Glennox, J. G., eds), pp. 137–169, University of Pittsburgh Press
Gaudilliere, J-P. (1992) *Hist. Phil. Life Sci.* 14, 23–71
Grmek, M. D. and Fantini, B. (1982) *Rev. Hist. Sci.* 35, 193–215
Keyes, M. E. *Stud. Hist. Philos. Biol. Biomed. Sci.* (in press)
Thieffry, D. and Burian, R. M. (1996) *Trends Biochem. Sci.* 21, 114–117
Witkowski, J. A. (1988) *Trends Biochem. Sci.* 13, 110–113

Recollections by scientists

Baltimore, D. (1995) *FASEB J.* 9, 1660–1663
Crick, F. H. C. (1988) *What Mad Pursuit*, Basic Books
Drake, J. W. and Crow, J. F. (1996) *Genetics* 144, 1–6
Hoagland, M. B. (1990) *Towards the Habit of Truth: A Life in Science*, W. W. Norton
Jacob, F. (1987) *La Statue Interieure*, Editions Odile Jacob (English edition: *The Statue Within: An Autobiography*, Basic Books)
Kornberg, A. (1989) *For the Love of Enzymes*, Harvard University Press
Luria, S. (1984) *A Slot Machine, A Broken Test Tube: An Autobiography*, Harper and Row
Nirenberg, M. W. (1969) *Nobel Lecture* (Vol. I, Pt 21), Nobel Foundation
Nomura, M. (1990) *Trends Biochem. Sci.* 15, 244–247
Spiegelman, S. (1978) *Tanpakushitsu Kakusan Koso* 23, 7–43
Watson, J. D. (1968) *The Double Helix*, Weidenfeld and Nicholson
Zamecnik, P. C. (1979) *Ann. New York Acad. Sci.* 325, 269–301

of the DNA. Methylation modifies the cytosine bases, and excess methylation often leads to transcriptional inactivity. In some cases, these patterns of methylation can be inherited and thus constitute a carrier of transgenerational information other than the sequence itself.

In a recent answer to a question addressing the relevance of these challenges, Crick stated that he still believes in the value of the Central Dogma today (F. H. C. Crick, pers. commun.). However, he also acknowledges the existence of various exceptions, most of which he regards as minor. For him, the most significant exception is RNA editing. Still, according to Crick, simplifications of the Central Dogma in terms such as 'DNA makes RNA, and RNA makes protein' were clearly inadequate from the beginning.

Discussion

Forty years after its initial formulation by Crick, the Central Dogma is still generally regarded as one of the keystones of molecular biology. However, popular textbooks and histories frequently overlook the contemporaneous controversies, conveying a success story rather than a story that includes numerous criticisms and corrections. Even though the history of molecular biology has been enriched recently by many new accounts (see Box 1), further examination of the history of the Central Dogma and its subsequent role in the development of molecular biology is necessary.

Beyond the Central Dogma's influence that we have noted here and heuristic value within Crick's own research programme, one question that remains open is that of the Central Dogma's heuristic role in the general development of molecular biology. Many of the discoveries that have followed the formulation of the Central Dogma (e.g. the characterization of transfer RNAs, the uncovering of the mechanisms of gene regulation and even the deciphering of the genetic code) came out of research programmes that had little or no connection to Crick's. Moreover, despite extensive efforts, the initial hope of a resolution of protein three-dimensional (tertiary) structure and function on the basis of the amino acid sequence has so far remained largely unrealized.

A closely related question is that of the definition of and the relevance of the concept of information in molecular biology. This question[34–36] goes well beyond the scope of this short historical review. However, in the light of present biological knowledge, we would like to mention here the necessity of distinguishing between at least three types of molecular biological information (or specificity): the information associated with the sequence itself; the specificity of the spatial conformation of macromolecules; and, finally, the information that can be associated with regulatory mechanisms (including epigenetic specifications such as methylation). Of the three, only the first was addressed explicitly by Crick in 1958. The conformational specificity (of proteins) was supposed to be derived directly from the sequence but was ultimately shown to depend on various other factors, including other proteins (e.g. chaperonins). The various mechanisms of gene regulation already characterized add a third

level of complexity that cannot be predicted solely on the basis of sequence or conformational information.

Curiously enough, the elucidation of the mechanisms of gene regulation in the late 1950s and early 1960s was rarely used in the criticisms of the Central Dogma or of the corresponding narrow conception of biological information. However, today, because regulatory mechanisms are known to involve almost any kind of biological molecule, either as targets or as effectors of regulation, a cell or an organism is increasingly considered to be a complex regulatory network. From this perspective, one might consider the Central Dogma effectively to be neglecting the feedback mechanisms present in the cell and thus lead to a simplified, but also much more accessible, scheme for the mechanisms controlling gene expression and protein synthesis.

Acknowledgements

We thank Richard Burian, Lily Kay, Evelyn Fox Keller, Michel Morange, Robert Olby, Hans-Jörg Rheinberger, Judy Johns Schloegel and Jan Witkowski for their critical reading of this paper and their many useful suggestions.

DENIS THIEFFRY

Max Planck Institute for the History of Science, Wilhelmstr. 44 10117 Berlin, Germany.

SAHOTRA SARKAR

Max Planck Institute for the History of Science, Wilhelmstr. 44, 10117 Berlin, Germany; and Dept of Philosophy, University of Texas, Austin, TX 78712-1180, USA.

References

1 Crick, F. H. C. (1958) *Symp. Soc. Exp. Biol. XII*, 138–163
2 Ephrussi, B., Leopold, U., Watson, J. D. and Weigle, J. J. (1953) *Nature* 171, 701
3 Mazia, D. (1956) in *Enzymes: Units of Biological Structure and Function* (Gaebler, E. H., ed.), pp. 261–278, Academic Press
4 Spiegelman, S. (1956) in *Enzymes: Units of Biological Structure and Function* (Gaebler, E. H., ed.), pp. 67–89, Academic Press
5 Lederberg, J. (1956) in *Enzymes: Units of Biological Structure and Function* (Gaebler, E. H., ed.), pp. 161–169, Academic Press
6 Pollock, M. R. (1953) in *Adaptation in Micro-organisms. 3rd Symposium of the Society for General Microbiology*, pp. 150–183, Cambridge University Press
7 Dounce, A. L. (1953) *Nature* 172, 541–542
8 Watson, J. D. (1965) *Molecular Biology of the Gene*, W. A. Benjamin
9 Olby, R. (1974) *The Path to the Double Helix*, Macmillan Press
10 Brachet, J. (1952) *Le rôle des acides nucléiques dans la vie de la cellule et de l'embryon*, Masson & Cie
11 Boivin, A. and Vendrely, R. (1947) *Experientia 3*, 32–34
12 Crick, F. H. C. (1970) *Nature* 227, 561–563
13 Crick, F. H. C. (1963) *Prog. Nucleic Acids Res. Mol. Biol.* 1, 163–217
14 Judson, H. F. (1979) *The Eighth Day of Creation,* Simon & Schuster (Expanded edition: Cold Spring Laboratory Press, 1996)
15 Watson, J. D. and Crick, F. H. C. (1953) *Nature* 171, 737–738
16 Jacob, F. and Monod, F. (1961) *J. Mol. Biol.* 3, 316–356
17 Rheinberger, H-J. (1997) *Toward a History of Epistemic Things. Synthesizing Proteins in the Test Tube*, Stanford University Press
18 Fraenkel-Conrat, H. (1956) *J. Am. Chem. Soc.* 78, 882–883
19 Gierer, A. and Schramm, G. (1956) *Nature* 177, 702–703
20 Jeener, R. (1956) *Adv. Enzymol.* 17, 477–498
21 Baltimore, D. (1970) *Nature* 226, 1209–1211
22 Temin, H. M. and Mizutani, S. (1970) *Nature* 226, 1211–1213
23 Commoner, B. (1964) *Nature* 203, 486–491
24 Commoner, B. (1968) *Nature* 220, 334–340
25 Witkowski, J. A. (1988) *Trends Biochem. Sci.* 13, 110–113
26 Morange, M. (1994) *Histoire de la Biologie Moléculaire*, La Découverte
27 Smith, C. W., Patton, J. G. and Nadal-Ginard, B. (1989) *Annu. Rev. Genet.* 23, 527–577
28 Gilbert, W. (1978) *Nature* 271, 501
29 Cattaneo, R. (1991) *Annu. Rev. Genet.* 25, 71–88
30 Koslowski, D. J. *et al.* (1990) *Cell* 62, 901–911
31 Prusiner, S. B. (1982) *Science* 216, 136–144
32 Keyes, M. E. *Stud. Hist. Philos. Biol. Biomed. Sci.* (in press)
33 Jablonka, E. and Lamb, M. J. (1995) *Epigenetic Inheritance and Evolution: The Lamarckian Dimension*, Oxford University Press
34 Keller, E. F. (1995) *Refiguring Life: Metaphors of Twentieth Century Biology*, Columbia University Press
35 Sarkar, S. (1996) in *The Philosophy and History of Molecular Biology: New Perspectives*, pp. 187–231, Kluwer Academic Publishers
36 Kay, L. E. *Who Wrote the Book of Life? A History of the Genetic Code*, Stanford University Press (in press)