

What history tells us

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The history of science was long considered to be something peripheral to science itself. By supplying interesting stories and gossip, it seemed, at best, to provide material for enlivening lectures. In general, it was deemed a suitable activity for retired scientists. This view has been revised considerably in the past years and indeed, today seems hopelessly out of date. History and philosophy of science are increasingly held to be an essential component of the education of scientists. By becoming acquainted with these areas, practicing scientists – and in particular biologists – can better appreciate the significance of the models and theories that underpin their research, especially with the accelerating succession of one idea by the next. The present series, of which the article that follows is the first, aims to give historical glimpses that bear on contemporary biology. The hope is that these glimpses will be both a source of inspiration and of help in resisting useless fashions.

I. The operon model and its legacy

1. Introduction

The year 2005 is the fortieth anniversary of the Nobel prize in physiology or medicine awarded to Professors François Jacob, André Lwoff and Jacques Monod for “discoveries concerning the genetic regulation of enzyme and virus synthesis”, better known as the proposal of the operon model and the discovery of messenger RNA. Jacob, Lwoff and Monod showed that the transcription of structural genes grouped on the genome into messenger RNA was controlled by the binding of a repressor – coded by a regulatory gene – on a DNA sequence located upstream of the regulated genes.

The anniversary of the discovery of the double helix structure of DNA, and the recent death of Francis Crick, have already offered occasions to commemorate such major discoveries that have led to the establishment of the paradigm of molecular biology, and represented – for those who made them – an explanation of the ‘secret of life’ (Morange 1998). Looking back at the discoveries made by Jacob and Monod is illuminating in a variety of ways. It highlights several, rarely described characteristics of the history of molecular biology, and of scientific discovery in general. Also it allows us to acknowledge the place their models have in our explanation of biological

processes, and casts light on some significantly new ambitions of post-genomic research programmes.

2. The origin of the model

The development of the operon model was made possible by the convergence of two different lines of research. One, led by Monod, concerned adaptive enzymes, in particular *b*-galactosidase, whose synthesis can be induced by lactose. Lysogeny – the process by which a bacteriophage can remain silently associated with a bacterium instead of lysing it – was simultaneously studied by Lwoff, Jacob and Elie Wollman (Judson 1979; Brock 1990). This convergence took the form of the famous PaJaMo experiment in which Arthur Pardee, Jacob and Monod used the genetic tools developed in the study of lysogeny to characterize the mechanisms of induction of *b*-galactosidase by lactose (Pardee *et al* 1959). Most historical studies have accorded pre-eminence to the lactose system (Gaudillière 1993), because of the more communicative personality of Monod, the abundance of historical documents on him, and the complexity of the work on lysogeny. As soon as one is able to overcome these obstacles, and to dive into the complexity of lysogeny, the landscape appears different: the study of temperate bacteriophages was obviously at

the heart of some of the most important ideas behind the operon model (Peyrieras and Morange 2002): (i) The idea of a repressor, controlling the 'inactive' form of the phage – the prophage –, was proposed long before the famous PaJaMo experiment showed the existence of a repressor in the lactose system. (ii) Jacob's idea that the repressor acts directly on DNA stemmed from the requirement for the repressor to block prophage development completely at an early stage. This idea of direct control at the level of the gene was made possible by the studies on bacteria and their viruses in the 1950s, but remained heretical for most geneticists, who considered that genes were controlling the cells in a distant and parsimonious way (Muller 1947), like a music conductor. (iii) The notion that co-regulated genes were grouped on the genome was far more evident for the phage than in the lactose system, where the number of genes was limited.

By according the study of lysogeny an important role in the construction of the operon model, we can better position this discovery in the general development of molecular biology. Even though Max Delbrück, the founder of the phage group, was for a long time reluctant to admit the existence of lysogeny, the contacts between the French and American phage researchers were close: the concepts and techniques were rapidly transferred from one system to another. Jacob, Lwoff and Wollman were full members of the small transnational community in which molecular biology emerged (Abir-Am 1993). The study of lysogeny aimed at characterizing the complex relations between a pathogen and its host: it therefore also belonged to the Pasteurian tradition of microbiology. The molecular description proposed by Wollman, Jacob and Monod was new, but clearly it was the culmination of efforts under way since the time of Pasteur and Koch. When viewed in the context of research on lysogeny, the advent of molecular biology was a smooth and progressive process, not a scientific revolution.

The decisive conceptual steps were made by Jacob in the Harvey Lecture that he gave in the summer of 1958, in which he established a relation between the results obtained in the PaJaMo experiment and his own studies on lysogeny (Jacob 1958). It is quite remarkable that this connection was probably helped by the constraints imposed on this lecture. Jacob had been asked to speak about "the genetic control of viral functions". At that time, he was committed to a very close collaboration with Monod on the lactose system. Jacob was therefore obliged to demonstrate that there was a connection between the two systems, and the rest, as they say, is history. We should all remember this whenever we grumble about the reviews or general talks we have to prepare!

Jacob and Monod are one of those famous pairs of scientists who contributed to the development of molecular biology, with Crick and Watson, and Meselson and Stahl

(Holmes 2001). In this case, as probably in others, the pairing was crucial to the achievement. Monod brought his extraordinary talent for critical review of the data and models. In addition, he had strength of purpose enough to focus all the efforts of both laboratories on the construction of the model.

3. The difficult acknowledgement of the legacy

The impact of the operon model was great, and its main characteristics are still a part of our "common biological knowledge": the expression of genes varies constantly, and is under the direct control of proteins – two ideas revolutionary at the time they were proposed. The paradox raised by Thomas Morgan in the 1930s – all the cells in a multicellular organism possess the same genes but do not have the same characteristics (Morgan 1935) – found in the operon model the beginning of an answer. This is why the operon model was a strong impetus for molecular biologists in the 1960s to turn to the study of higher organisms and their development. With the operon model, they had the conceptual tools needed to explain what happens during differentiation and development. The operon model had a major role in the progressive emergence of the developmental gene concept in the 1970s (Morange 2000a).

Nevertheless, the operon model went out of fashion in the 1970s and 1980s, and the major breakthrough it was is not yet fully recognized. There are various, indeed opposite, reasons for this oversight. The success that immediately greeted the operon model, and its use to explain every biological phenomenon – including cell differentiation (Waddington 1962) and cancer (Comings 1973; Morange 1997) –, in most cases without any supporting data at the time, probably constitute one reason. A second reason was the dogmatic attachment of Monod to a negative form of regulation, and his reluctance to admit the existence of positive regulation. It was also rapidly shown that in most organisms – except bacteria – co-regulated genes are not usually grouped together on the genome. Another reason was the ambiguous role played by the notion of genetic programme. This notion, proposed by Jacob and Monod (1961) and simultaneously by Ernst Mayr (1961), immediately became very fashionable, but was later criticized by some biologists and philosophers (Keller 2000). For the critics, it became emblematic of the 'errors' of molecular biologists, and of their naive vision. One must nevertheless point out that the notion of genetic programme targeted for criticism was in the main invented by the critics themselves, and does not correspond to the metaphorical use of this notion made by most molecular biologists, including Jacob (Morange 2000b).

Thus, following an initial very favourable reception, the operon model came to be criticized at the end of the 1960s by embryologists, including Conrad Waddington (1969), who argued that the simultaneous regulation of hundreds or thousands of genes during differentiation and development required new models, distinct from the operon model. Some embryologists may have found it difficult to admit that the problems they had studied all their professional lives could be solved by people – molecular biologists – who worked on bacteria and bacteriophages, and this seems to be a plausible explanation of their attitude. The speculative Britten-Davidson model of gene regulation (which in retrospect has not had the general value its authors attributed to it) was at that time considered by many as more attractive than the operon model (Britten and Davidson 1969). Epigenetic mechanisms such as DNA methylation and chromatin modifications were intensively studied in the 1970s as possible mechanisms for differentiation; they were looked at as alternatives to the operon model (Morange 2002). During the last decade, however, instead of remaining in conflict, the regulation of gene expression by transcription factors and epigenetic modification has become part of the same conceptual framework.

Finally, full recognition of the explanatory power of the operon model was probably hampered by the long time needed to confirm the model's predictions in higher organisms. It was not until the late 1970s that suitable molecular tools became available. When homeotic genes were characterized, two decades had passed, and a new generation of molecular biologists was active. The outcome was a confirmation of the anticipations of Jacob and Monod regarding the major role that regulatory genes might have in development. For this new generation, the control of gene expression by regulatory proteins was so evident that it was no longer necessary to refer to the founding model and experiments.

4. Post-genomics and the operon model

The first studies of the transcriptome with DNA chips led to a resounding recognition of the anticipations of Monod and Jacob on the molecular mechanisms involved in differentiation and development (Niehrs and Pollet 1999). The complex regulatory circuits generated from these data are not very different from those proposed by Monod and Jacob a few months after their publication of the operon model, in the conclusion to the 1961 Cold Spring Harbor symposium (Monod and Jacob 1961). A formal, mathematical description of these regulatory circuits has been the subject of intense efforts recently (Ozbudak *et al* 2004). One of their characteristics, which is now under scrutiny, is their dynamic behaviour; in particular, the

aim is to explain the hysteretic effects observed in these systems, and their ability to function in a bistable – fully active or fully inactive – manner.

The possibility of a dynamic behaviour for these regulatory genetic networks did not escape the attention of Monod and Jacob. Nevertheless, they, and until very recently molecular biologists in general, paid scant attention to efforts to model the behaviour of these circuits through a logical or dynamic approach (Thomas 1981). One may wonder at this lack of interest. The need for precise measurements of the different parameters of the system and for experimental tools to manipulate them before modelling is insufficient to explain the delayed recognition of these efforts. The main reason is probably cultural, residing in the difficulty for someone brought up in the ethos of molecular biology to understand that a precise, quantitative description of processes inside cells and organisms constitutes part of the explanation. The more accepted attitude is that a qualitative description of the causal pathway going from a signal to its targets in terms of interactions between macromolecules is a satisfactory explanation: the characterization of the strength and duration of these interactions is not considered as necessary to understand what happens. What is new in biology today is the more general acknowledgement of the importance of the quantitative approach to biological phenomena, linked to the elaboration of formal models. This interest, and not the associated new technologies, constitutes the essence of the post-genomic era.

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