A night at the operon

The *lac* Operon: A Short History of a Genetic Paradigm
by Benno Müller-Hill
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This book opens with the lament that for young molecular biologists history does not exist, and that they have no interest in the long struggle that has made the subject what it is today. I hold the somewhat weaker view that history does exist for the young, but is divided into two epochs: the past two years, and everything that went before. That these have equal weight is a reflection of the exponential growth of the subject, and the urgent need to possess the future and acquire it more rapidly than anybody else does not make for empathy with the past.

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The three winners: François Jacob, Andre Lwoff and Jacques Monod receiving the 1965 Nobel Prize for Physiology or Medicine for their research into the genetic control of enzyme activity.

Benno Müller-Hill says that "one has to grow old to understand the functioning of a science". He has written a history of the *lac* system of *Escherichia coli*. He warns us that it is not a definitive history, which comes as a relief because that kind of history would have been boring. What Müller-Hill has written is partly historical, partly autobiographical, and even partly philosophical. It is best described as a collection of stories (with a few parables, too) disguised as a history of what is now a small and almost unoccupied corner of molecular biology.

About 30 years ago the *lac* operon stood in the centre of the scientific stage, and provided the experimental basis for discovering the principles of the control of gene expression. Parallel research on the *lac* operon and bacteriophage λ formed the basis for the operon theory of gene regulation put forward by François Jacob and Jacques Monod in 1961. One central idea was that regulation was negative, that is, if the genes were placed in a control vacuum they would be unleashed and express as much as they could. Their expression was held back by repressors, and they were turned on by the removal of repression, either by an inducer in the case of the *lac* genes, or by destruction of the repressor in bacteriophage λ. Repressors were later found that required a small molecule to make them active so they could turn off their target genes.

So central was this idea of negative control that it became established doctrine, and those few scientists who worked on positive regulation were dismissed and had to struggle for a hearing. It was later found that cap factor acts positively on the *lac* operon, and that the λ repressor exerts a positive effect on its own synthesis, so the dogma of negative control gradually disappeared.

Evidence for the theory came from the discovery of operator-constitutive mutants, which were *cis* dominant, affecting the regulation of both β-galactosidase and lactose permease on the same chromosome. The realization that virulent mutants of bacteriophage λ were equivalent reinforced the conclusion that they had to affect a site on the DNA that interacted with the repressor and controlled the expression of two different genes. Operator-zero mutants also acted in *cis*, but these were later shown to be due to nonsense mutants with strong polarity; they had nothing to do with operators but nevertheless required the idea of the operon, a unit of expression containing more than one gene.

Müller-Hill and Walter Gilbert succeeded in isolating the *lac* repressor in 1966. This was quite an achievement, as the only assay for this repressor was that it bound the inducer, IPTG, and calculations showed that the value of the binding constant and the number of repressor molecules would not allow detection by equilibrium dialysis. Müller-Hill selected for a mutant that had a higher affinity for the inducer than the wild-type repressor and this tight-binding mutant made the experiments feasible.

The contemporary student finds it hard to understand that this research always had to be carried out by indirect means, and not by looking directly at genes as we do today. The design and interpretation of such experiments was the core skill of molecular biology, and critical experiments often resorted to what Francis Crick once called "special genetic tricks", a primitive kind of genetic engineering. It was also important to ensure that theories did more than explain the facts on which they were based, and to distinguish prediction from retrodiction.

The move to research on eukaryotes began at the end of the 1960s, and prokaryotic research started to decline. We argued for many years about whether the Jacob–Monod model would have anything to do with cell differentiation in higher organisms, and it is ironic that positive regulation is generally found, with many transcription factors acting to enhance gene expression. There was disappointment at the general absence of operons and the resulting unitary control of a group of genes by one operator. What has survived, though, is the central principle that regulation is mediated by specific recognition of DNA sequences by proteins.

When molecular biology finally comes to an end, and a massive crash of the computer system in the library at Alexandria corrupts most knowledge, I hope that historians of science will unearth a copy of this book. They will surely debate whether all of the stories are true and whether they could have been written by the same person, and might even suggest that Müller-Hill was at least two people. What will certainly puzzle them is that it is full of characters they have never encountered before, and that even the famous ones are hard to recognize. The only thing they will learn about Watson and Crick is that the former produced a naked lady for the latter's fiftieth birthday. Was this perhaps part of some obscure symbolic ritual enacted each year to celebrate the birth of another model? □

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