

The Return of the Blue Unicorn

Book Review

The *lac* Operon

By Benno Müller-Hill.

Berlin: Walter de Gruyter. (1996). 207 pp. \$35.95.

The very first paper I give to students in my yearly course on microbial genetics is an article on conditional lethal mutants by Norman Horowitz and Urs Leupold from the 1951 Cold Spring Harbor Symposium (Horowitz, N. H., and Leupold, U. [1951], Cold Spring Harbor Symp. Quant. Biol. 16, 100–110). The following passage always stops us: "...in which case the one gene–one enzyme hypothesis must be banished to the purgatory of untestable hypotheses, along with the proposition that a blue unicorn lives on the other side of the moon." We wonder at the fanciful language. What is it doing in a scientific paper? How did it get past the referees? If members of his study section read it, did Horowitz get his next grant? We shouldn't wonder. This more personal writing style represents a mode of scientific writing that was much more common in the past, but is quite alien to us today. Remember Watson's and Crick's amusingly, if not arrogantly, understated "... it has not escaped our notice...." (Watson, J. D., and Crick, F. H. C. [1953], Nature 171, 737–738). The personality of the scientist was often right there on the written page. Today it is rare to find any trace of the author in a scientific article except when an elder statesperson recounts his or her glorious career.

So, it is truly refreshing to read through Benno Müller-Hill's *The lac Operon*, a thorough recounting of the history of this paradigmatic regulatory system, the knowledge of which he traces back 4000 years ago to Noah. Many people may be annoyed or even offended, as I was, by some of the passages, but we should thank him for reminding us that this work was done by personalities. And the personality we get the most feel for is Müller-Hill himself. It is palpable on almost every page. In describing various research accomplishments and their authors, he is alternately gracious, enthusiastic, adulatory, dismissive, sometimes arrogant, and finally philosophical and political. Remember, Müller-Hill also wrote *Murderous Science* ([1988] Oxford University Press, New York), in which he documents how, early in this century, German doctors and scientists promoted and participated in eugenical and ultimately genocidal policies, even well before the Nazis took power.

The lac Operon is divided into three sections. The first covers the history of studies on the system (from Noah) pretty much up to the dawning of the recombinant DNA era in the 1970s. Perhaps the most unusual feature of this book is its middle section, which comprises 24 chapters on errors made over the years in the study of the *lac* operon. The final section summarizes research over the last twenty years where modern technological developments have resulted in deeper understanding of the system ranging from the structure of β -galactosidase to the details of interactions at the *lac* promoter. It ends with two poems from Goethe.

The chapters generally run to no more than 4 pages

and are often only 1 or 2. This pointillist form of science writing has the same effect as its canvas counterparts—it lends luminosity and coherence to the field of *lac* operon research as a whole by combining a set of short focused stories. These chapters often resemble a series of moral tales. They include dicta such as "anything not forbidden is compulsory," "old ideas die with those who propose them," and "do not believe an old scientist when he says something can never be done." Scientific findings are mixed in with such facts as Monod's participation and subsequent disaffection from the Communist party, Gilbert's comfortable upbringing compared with the travails of a young Sverdlov, who was the first to present the idea of chemical DNA sequencing, and the death of one of Müller-Hill's students in an avalanche in the Alps. One striking aspect of the book is that these stylistic features seem to disappear in the last section. The scientists suddenly become faceless. Has personality disappeared from their lives as well as their writing?

I come back to the middle section where Müller-Hill summarizes the many wrong turns that were taken in studies on the *lac* operon. Despite the criticisms I will make of this portion of the book, I consider it an extraordinarily valuable addition to the scientific literature. This section is unusual in that scientific texts ordinarily present the current version of the truth and thereby suggest a steady uninterrupted progression in scientific studies. False steps are ignored. The result is a misrepresentation of scientific progress and a missed opportunity to give both the science student and the layperson a more accurate picture of science. In introducing this section, Müller-Hill points out that errors are often made because of faulty assumptions. If he had proceeded to analyze his 24 "misinterpretations" in these terms, this section would have been particularly useful. Unfortunately, more often than not, one gets the sense that Müller-Hill considers that a lot of the mistakes were made out of pure stupidity. The analysis should be much richer than that! Such descriptors of the basis of errors as "self-delusion," "non-rational," or "ugly model" don't help. Some of these errors may seem really foolish in retrospect, but it is important to put them in the context of the period in which they were made and analyze the assumptions within the field at the time. Furthermore, as Müller-Hill points out, some of the wrong proposals for *lac*, such as repression at the level of translation, regulation via RNA molecules (antisense regulation), and catalytic RNAs, proved correct for other systems. And what about the errors made by people who were right? A rereading of the deservedly classic "correct" paper by Pardee, Jacob, and Monod, where the repressor is first proposed, reveals that nearly all the arguments from *other* systems used in the discussion to reinforce the idea of negative control are wrong (Pardee, A. B., Jacob, F., and Monod, J. [1959], J. Mol. Biol. 1 165–178). In fact, given our more detailed current knowledge of genetic regulation, we now know that all of their own results presented in the paper can also be explained in terms of positive control. Intuition, aesthetics, historical moment,

and personalities played a large role in the rapid acceptance of the theory (Beckwith, J. [1996], In *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology*, F. C. Neidhart et al., eds., ASM Press, Washington, D.C., 1227–1231).

The author of a scientific text has the opportunity to present his or her view of scientific truth. The reviewer has the opportunity to correct misinformation, and when that misinformation is about the reviewer's own work, it is hard to resist the opportunity to set the record straight. In 1966, John Scaife and I presented the first genetic scheme for obtaining promoter mutants and pursued it with the *lac* operon (Scaife, J., and Beckwith, J. R. [1966], Cold Spring Harbor Symp. Quant. Biol. 37, 403–408). Our successful isolation of these mutants allowed us to define and locate a promoter for the first time. So, it was disappointing to read on page 50 that this feat was accomplished by my scientific idols Jacob and Monod. That error aside, let me say that this is a book to be celebrated. Müller-Hill's obvious enthusiasm for science and for the *lac* operon in particular is infectious. To those millenarians like Gunther Stent (Stent, G. S. [1978], *Paradoxes of Progress*, W. H. Freeman and Company, San Francisco) and John Horgan (Horgan, J. [1996], *The End of Science: Facing the Limits of Knowledge in the Twilight of the Scientific Age*, Addison-Wesley, Reading, Massachusetts) who argue "the end of science," Müller-Hill envisions 100 more years of research on this old chestnut—the *lac* operon. While this may be a bit optimistic, this book does illustrate how the focus of the research community on a single system has yielded and continues to yield new insights into biology.

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