Reflections
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**The Early Influence of the Institut Pasteur on the Emergence of Molecular Biology**

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I met Jacques Monod for the first time in September 1944. The 4 years of the hellish Nazi occupation of France were over. Jacques was still wearing the uniform of an officer of the French Army. I was 24 years old and had a relatively limited research experience: six months in the Laboratory of Animal Physiology at the Sorbonne (1939–1940), a few months in the Laboratory of Pharmacology at the Pharmacy School of the University of Montpellier (1941), a few months in the Department of Biochemistry of the Medical School in Marseille (1942), and a year in the Department of Biochemistry of the Institut Pasteur (1943–1944). These activities were interrupted by the military service, a few weeks of captivity, an escape, my marriage, and the birth of my first child. This should explain my lack of professional training and my great desire to find a person who could help me. Jacques Monod became rapidly my mentor.

In 1946, Lwoff and Monod went together to the Cold Spring Harbor Symposium on Heredity and Variation in Microorganisms. This symposium reinitiated a series after a 3-year interruption imposed by the war emergency. It could have been held in the summer of 1945 but was postponed for a year because of travel restrictions. This delay was a fortunate one because whereas the genetics and physiology of microorganisms had made remarkable progress in the laboratories of the United States, when the contacts were reestablished it was found that many discoveries in the same field had been made in Western Europe. As a consequence, the scope of the program was considerably broadened. In addition to Lwoff and Monod, the French contingent included Latarjet and Ephrussi. The symposium presented several important discoveries such as the findings of Anderson, Delbrück, Bailey, and Hershey in phage genetics; those of Lindegren and Pontecorvo on yeast and fungal genetics; and those of Luria, Lwoff, Tatum, Demerec, Latarjet, and Ryan on bacterial mutability. There was also a two-page report by Joshua Lederberg in which bacterial recombination was elegantly demonstrated. However, above all the meeting represented, to echo Seymour Cohen, the emergence of a major young and new scientific community after World War II.

The origin of the β-galactosidase saga can be traced back to the doctoral thesis of Jacques Monod, published 60 years ago, and devoted to the study of bacterial growth. During these studies begun in 1937, Monod had observed that when *Bacillus subtilis* or *Escherichia coli* were grown on a mixture of two particular sugars, growth occurred in two distinct phases separated by a lag time. During the first phase only one of the two sugars was metabolized, and the second began to be degraded only when the first sugar had totally disappeared. Glucose was found to belong to the first category and lactose to the second (1, 2).

A few days after I first met Jacques Monod, he described to me his experiments on this diauxic growth and told me that it might take 20 years or more before this observation receives a molecular explanation, but he was determined to accept the challenge (Fig. 1). During the 1940s, several theories tried to explain the phenomenon of enzymatic adaptation such as the functional hypothesis, where the inducer acts as a substrate, or the equilibrium hypothesis, where it displaces the equilibrium between an inactive precursor and the active enzyme.

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Monod and his colleagues Annamaria Torriani, Melvin Cohn, and Germaine Cohen-Bazire eliminated these theories by a series of convincing experiments. With Melvin and David Hogness, he demonstrated that the induced enzyme is synthesized de novo from free amino acids, themselves deriving from the carbon source.

I joined Monod’s laboratory in 1954 after having spent my first research years on the mechanism of bacterial fermentations and contributing to the elucidation of some amino acid biosynthetic pathways in *E. coli*. Jacques asked me to see whether after addition of labeled thiomethylgalactoside, a non-metabolizable inducer, radioactivity could be found linked to one of the macromolecular components, DNA, RNA, or protein. In retrospect, this naive experiment had no chance of succeeding. It required the concept of a specific Lac repressor, only proposed in 1964 by Pardee, Monod, and Jacob, and a more sophisticated technology than our primitive methods of enzyme activity measurements and the use of Petri dishes to follow the result of bacterial conjugations. Ultimately, Gilbert and Müller-Hill isolated the repressor in 1966, transforming a concept into a bona fide molecule and answering the question Monod had asked me to study. However, the experiments I carried out with Howard Rickenberg and Gérard Buttin brought interesting fringe benefits; the amount of intracellular radioactivity was negligible in non-induced cultures but very high in cultures that had been pre-induced by growth in the presence of a galactoside. We developed with Jacques Monod the concept of a catalytic permease, which was not readily accepted by the establishment (3–5). It was not until many years later that Benno Müller-Hill wrote me with the news that he had cloned and sequenced the lactose permease (6). I think that our work contributed to opening the field of a molecular approach to cellular permeability, so ably continued by E. Kennedy, R. Kaback, S. Roseman, G. Ferro-Luzzi Ames, and many others. During our work we noticed that mutants that were constitutive for β-galactosidase were also constitutive for β-galactoside permease, establishing that the inducible to constitutive mutation was pleiotropic (4, 5). We named the corresponding alleles $i^+$ and $i^-$. In 1959, Irving Zabin and Adam Képès added a third member, the gene for thiogalactoside transacetylase to the two genes whose expression was governed by the $i$ gene (7). Monod, Jacob, and their associates found that the three genes were linked, forming a coordinate unit of transcription, which they called an operon. They hypothesized that the product of the $i$ gene, the repressor, was bound to a DNA structure, the operator,
upstream of the operon’s structural genes (6). This hypothesis was later totally substantiated by W. Gilbert and B. Müller-Hill in 1966 and 1967, who isolated the Lac repressor (8) and characterized its target operator sequence (9). In 1959, the repressor hypothesis was extended to the regulation of biosynthetic enzymes by myself and Jacob, working on the tryptophan biosynthetic enzymes (10). This work was beautifully extended by Charles Yanofsky in the United States; his studies on the expression of the tryptophan genes led him among other discoveries to unravel the phenomenon of attenuation (11).

In 1968 Ullmann and Monod (12) simultaneously with Perlman and Pastan (13) showed that the catabolic repression exerted by glucose on β-galactosidase synthesis is reversed by cyclic AMP, opening the way to a molecular explanation of diauxy.

The three-dimensional structure of β-galactosidase (14) provides an explanation for the α-complementation first observed by Ullmann, Jacob, and Monod almost 40 years ago (15) and which, apart from its theoretical interest, forms the basis of the familiar blue-white selection process for recombinant DNA routinely used in both prokaryote and eukaryote research.

After my incursion in the field of galactosidase and permease, I returned to the study of the regulation of the activity and of the synthesis of amino acids in E. coli, influenced by the intellectual atmosphere present in Monod’s laboratory and by a 6-month decisive collaboration with Earl Stadtman who came to Paris during a sabbatical period, during which we started to elucidate the regulation of the synthesis of the amino acids of the aspartic acid family in E. coli (16), a subject that was going to keep me busy for the rest of my scientific life.

In 1960, I created the Laboratoire d’Enzymologie of the Centre National de la Recherche Scientifique at Gif sur Yvette near Paris. I was joined by Jekisiel Szulmajster (Kissel) and by his wife Huguette de Robichon-Szulmajster and enjoyed the presence of numerous students, among which I must cite Jean-Claude Patte, Paolo Truffa-Bachi, Joel Janin, and Michel Véron and of distinguished visitors, in particular Gordon Tomkins, Ed Adelberg, Mike Doudoroff, and Roger Stanier. I continued, however, to maintain close relationships with the Pasteur Institute, where I returned in 1969 to take over the Laboratoire de Physiologie Microbienne when André Lwoff retired. When Jacques Monod became the Director of the Institut Pasteur, he asked me to become his successor as Head of the Laboratoire de Biochimie Cellulaire, where I worked until my official retirement in September 1989 at the age of 70.

During the period between 1947 and 1960, the laboratories of Lwoff, Jacob, and Monod enjoyed the presence of many foreign visitors who came to one of the meccas of modern biology. The first American visitor to come to the Institut Pasteur was Seymour Cohen in 1947, followed by Michael Doudoroff and Melvin Cohn. Other visitors in Monod’s laboratory were Martin Pollock, Alvin Pappenheimer, Aaron Novick, Bernard Davis, Arthur Koch, Stuart Edelstein, David Hogness, Howard Rickenberg, Leonard Herzenberg, Bernard Horecker, Frederick Neidhardt, Maurice Sussman, Donald Brown, Boris Magasanik, Edmond Fischer, Roger Stanier, Harlyn Halvorson, Arthur Pardee, Earl Stadtman, John Beckwith, Irving Zabin, Dean Cowie, and Robert Rownd. The discovery of lysogeny by Lwoff and the classical analysis of sexuality by his young colleagues, Wollman and Jacob, brought to our laboratory a host of bright scientists among whom I remember Lane Barksdale, Louis Siminovitch, Niels Kjeldgaard, Dale Kaiser, Julius Marmur, Cyrus Levinthal, Seymour Benzer, Gunther Stent, David Shemin, Allan Campbell, Edwin Lennox, Walter Gilbert, Jerard Hurwitz, Edward Adelberg, C. B. van Niel, Jim Darnell, Sol Goodgal, Neal Groman, Bruce and Giovanna Ames, and Ethan Signer. All contributed their knowledge and took advantage of ours.

It was during that period that the concept of messenger RNA originated with the experiments carried out by Brenner, Jacob, and Meselson (18) and those performed by the group of Gros and Hiatt at the Institut Pasteur in collaboration with Gilbert, Kurland, and Watson at Harvard (17).

Personally, I have been present in Monod’s laboratory from 1954 to 1960, but I sincerely think that a few individuals only have witnessed the birth of as many fundamental biological concepts in such a short period and in a single laboratory. This was due in great part to the outstanding personality of Jacques Monod and to the atmosphere he was creating around him, generating a climate of constant stimulation and fruitful discussions.

If one is interested in the phylogeny of ideas, it can be said that the early findings at the Institut Pasteur recalled above lie at the origin of present day interest in molecular interactions. These studies have led in other laboratories to the determination of the structure of many DNA-protein and DNA-protein-effector binary and ternary complexes, which have
provided or will provide a rational explanation for the regulation of transcription in both prokaryotic and eukaryotic organisms.

Time has elapsed; today promoters, operons, messenger RNA, repressors, and allosteric enzymes are part of our scientific culture. The majority of the present day biologists started their work after 1980 when genetic engineering allowed the isolation and characterization of genes. The period between 1940 and 1963, where the concepts of molecular biology were painfully born, belongs for the new generation of biologists to another world where the tools of investigation were totally different. Still, although being conscious of the evolution of science, I look backwards with nostalgia to these exceptional decades.

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REFERENCES

1. Monod, J. (1941) Sur un phénomène nouveau de croissance complexe dans les cultures bactériennes. C. R. Acad. Sci. (Paris) 212, 934–936
2. Monod, J. (1942) Recherches sur la croissance des cellules bactériennes. Ph.D. thesis, Actualités scientifiques et industrielles, Hermann Paris
3. Cohen, G. N., and Rickenberg, H. V. (1955) C. R. Acad. Sci. (Paris) 240, 466–468
4. Rickenberg, H. V., Cohen, G. N., Buttin, G., and Monod, J. (1956) Ann. Inst. Pasteur 91, 829–855
5. Cohen, G. N., and Monod, J. (1957) Bacteriol. Rev. 21, 169–194
6. Büchel, D. E., Gronenborn, B., and Müller-Hill, B. (1980) Nature 283, 542–545
7. Zabin, I., Képès, A., and Monod, J. (1959) Biochem. Biophys. Res. Commun. 1, 289–292
8. Gilbert, W., and Müller-Hill, B. (1966) Proc. Natl. Acad. Sci. U. S. A. 56, 1891–1898
9. Gilbert, W., and Müller-Hill, B. (1967) Proc. Natl. Acad. Sci. U. S. A. 58, 2415–2421
10. Cohen, G. N., and Jacob, F. (1959) C. R. Acad. Sci. (Paris) 248, 3490–3492
11. Yanofsky, C. (1981) Nature 289, 751–758
12. Ullmann, A., and Monod, J. (1968) FEBS Lett. 2, 57–60
13. Perlman, R., and Pastan, I. (1968) Biochem. Biophys. Res. Commun. 30, 656–664
14. Juers, D. H., Jacobson, R. H., Wigley, D., Zhang, X-J., Huber, R. E., Tronrud, D. E., and Matthews, B. W. (2000) Protein Sci. 9, 1685–1699
15. Ullmann, A. (1992) Bioessays 14, 201–205
16. Stadtman, E. R., Cohen, G. N., LeBras, G., and de Robichon-Szulmajster, H. (1961) J. Biol. Chem. 235, 2033–2038
17. Gros, F., Gilbert, W., Hiatt, H. H., Attardi, G., Spahr, P. F., and Watson, J. D. (1961) Cold Spring Harbor Symp. Quant. Biol. 26, 111–132
18. Brenner, S., Jacob, F., and Meselson, M. (1961) Nature 190, 576–581
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