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Jacques Monod – A theorist in the era of molecular biology / Un théoricien à l'ère de la biologie moléculaire

A faith in the coherence of the living world

La foi dans la cohérence du monde vivant

Henri Buc

Institut Pasteur, 25-28, rue du Docteur-Roux, 75724 Paris cedex 15, France

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ABSTRACT

In this review, I compare the development of Monod's intellectual leadership in two fields, the regulation of enzyme biosynthesis and the control of enzymatic activity. I characterize the comings and goings between his scrupulous analysis of a given model system, his ability to compare the outcome with very distant experimental results, his audacity in formulating, then a physical interpretation of this convergence through a unifying mechanism. Finally, I briefly discuss how his attitude has durably impacted the whole field of molecular biology.

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RÉSUMÉ

Dans ce texte, je compare comment s'est établie la prééminence intellectuelle de Jacques Monod dans deux champs de recherches, la régulation de la biosynthèse des protéines et le contrôle de l'activité enzymatique. Je caractérise les allers et retours qu'il a pratiqués entre une analyse scrupuleuse de quelques systèmes particulièrement bien choisis, sa capacité à les mettre en relation avec des résultats expérimentaux de natures tout à fait différentes, son audace pour formuler alors une interprétation physique des convergences observées, à travers des mécanismes unificateurs. In fine, je discute comment cette attitude a durablement affecté le champ entier de la biologie moléculaire.

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1. Introduction

In one of the most quoted passages of *The statue within*, François Jacob explained that he learned from Francis Crick "not to quail about the boldness of a hypothesis; the process of experimental science does not consist in explaining the unknown by the known, as in certain mathematical proofs. It aims on the contrary to give an account of what is observed by the properties of what is imagined. To explain the visible by the invisible". Few pages below, he characterizes Monod's style as "a mixture of logic and passion, of tenacity along a single track, and probing thrusts in every direction. [Monod was] haunted by the need to look for the truth of nature and to make it known... More than confidence, he had faith in this nature, in its coherence, its unity" [1].

The purpose of this essay is to characterize the boldness with which Jacques Monod proceeded in two of the most significant discoveries he made with his close collaborators, the regulation of enzyme biosynthesis, the indirect control of enzymatic activity by effectors. These episodes

Email address: henri.buc@pasteur.fr.

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are well known and have been extensively commented (see, for example, [2,3]). I am revisiting here not only his famous final papers, but also the documents we have kept on their elaboration inquiring how tightly are linked in his case the audacity of his style of investigation and his faith in the coherence of the living processes.

2. From enzyme induction to the repressor hypothesis

Microorganisms adapt their metabolism according to the carbon source to which they are exposed. The phenomenon of enzyme adaptation – how the enzymatic activity enabling nutrient assimilation is established – was studied by Monod on the specific case of lactose utilization. True induction operated immediately, triggered by components bearing some chemical similarity with the substrate to be degraded. In the so-called constitutive strains, a specific mutation could restore the ability of the bacteria to produce the enzymatic system, even in the absence of an added inducer. For Monod, the challenge at stake was to understand "the respective roles of the inducing substrate and of the specific gene (or genes) in the formation and the structure of the enzyme" [4].

Monod devoted all his energy to this simple but impressive challenge. He assembled around him a team of competent people, bringing to the Institut Pasteur all the skills they could provide in a generous and friendly atmosphere. Though the experimental work of the group was not exclusively devoted to the adaptation of lactose utilization, one can follow his methodology by focusing on this sole example. On the biochemical side, he showed that expression of β-galactosidase enzymatic activity – the main protein responsible for lactose utilization – reflected the completion of its synthesis from its amino acid components. Chemistry was then solicited: synthesis of dozens of analogs of the enzymatic substrate was performed, and each of them was assayed as a potential substrate, inhibitor or inducer, leading to the first great surprise: there was no correlation whatsoever between the catalytic efficiency displayed by a given compound and its regulatory power, as if the two functions were under the command of two different templates in the cell. These two experiments were inconsistent with a common view prevailing at the time, where the role of the inducer acting as a substrate analog was supposed to convert an inactive precursor of β-galactosidase into an active enzyme.

On the genetic side, the fabulous expertise developed in Lwoff's unit was systematically adapted to the study of the lactose system. The lambda bacteriophage had already been used as a gene carrier to generate transient diploids for mapping purposes. Transposition of this methodology to the *lac* system by Jacob and Monod's group showed that the *z* and *y* genes responsible for lactose utilization were distinct from *i*, the one conferring sensitivity to the inducer. The synergy between genetic and biochemical studies culminated in the Pajamo experiment: bacteriophages carrying the various combinations of *i* and *z* genes were injected into recipient bacteria possessing the complementary set of alleles. The analysis of the ensuing expression of β-galactosidase activity showed that it was the i^+ allele that was functional. It maintained the system in the "off state", exerting a dominant effect on its impaired i^- allele. Furthermore, in this experiment, switching off the system could be either immediate or could take time, depending on the precise disposition of the two sets of alleles, present on the chromosome of the recipient cell and on the injected phage. When the phage injected the i^- and z^- alleles into a recipient i^+z^+ bacterium, no β-galactosidase activity was observed, the recipient i^+ gene exerting permanently its negative effect on enzymatic expression. When the combination of donor and recipient genes was inverted in the assay, the injected phage triggered β-galactosidase enzymatic activity at a maximal rate in a first phase. The negative regulation exerted this time by the injected i^+ gene took place along a second, slow phase. This slow process was completely abolished if an inducer had been previously added to the culture medium. The only difference between the two assays was the previous history of the recipient bacteria. Their cytoplasm had to contain an active principle in the first case, while the synthesis of this agent took time in the second experiment. In summary, the i^+ gene had to exert a repressive action, arising from a cytoplasmic product. This action was relieved when an inducer molecule was present in the culture medium.

This dry account misses an important point; these experiments did not develop in isolation. From the very beginning, a parallel was systematically drawn by Monod between the control of the induction process in the *lac* system and that exerted on amino acid biosyntheses. Experiments and comparisons were simultaneously performed on these different systems. The final explanation reached on the *lac* system through the Pajamo experiment applied as well to these other cases if the control gene was still supposed to encode a repressor, but if the role of the regulating metabolite was inverted, it had no longer to act as an anti-repressor, but as a co-repressor, required for turning off the biosynthesis of the specific enzymes involved. Indeed, recalling his attitude during this exploratory phase, Monod claimed: "faith (was) established a long time before I would be able to achieve certainty" [4]. He progressively established a common experimental strategy to reach this goal in all these different cases. As pointed out by Jon Beckwith, "the approaches (followed in the *lac* case) presented a model not only for a mechanism for gene regulation but also for *how* to study gene regulation" ([5], see also [6]).

Furthermore, it also appeared in the same period that the repressor model not only accounted for the regulation of protein syntheses in repressible and in inducible systems, but also for the biosynthesis of specific phage proteins early expressed after the induction of lysogenic bacteria. As it became clear to Jacob a few months afterwards, the Pajamo experiment paralleled an earlier observation made by Wollman and himself in 1956 as they were performing reciprocal crosses between non-lysogenic bacteria and bacteria carrying a prophage. The outcome strictly depended on whether the prophage was carried by the donor or by the recipient bacteria, as in the initial phase of the Pajamo experiment. The prophage was at once induced if and only if it was the male cell that carried the prophage. Why not then to assume, that again the presence

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