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Monod before Monod: Enzymatic Adaptation, Lwoff, and the Legacy of General Biology

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ABSTRACT - For most of his scientific career, Jacques Monod appeared to be a man of a single problem: the formation of enzymes and the regulation of their properties. His ability to produce theoretical models led him to play a major role in both the discovery of the operon regulation and the model of allosteric transitions. The successes of Monod, from the 1950s to the Noble Prize (1965), are already well documented. In this paper, I will focus on the Monod before Monod, that is, the Monod who, during the 1940s, tried to explain the fundamental phenomenon of enzymatic adaptation. To begin with, however, I will survey how this phenomenon was discovered and explained by French Pasteurians at the very beginning of the twentieth century. This first explanation took place amidst an entrenched Lamarckian atmosphere in French thought, which was still alive during the 1920s and the 1930s, when Monod commenced the study of biology at the Sorbonne. Because of his will to construct a scientific biology free from teleology, Monod always tried to break from the legacy of this traditional background of Lamarckism, and he consequently developed ways of thinking that, in the main, were not part of the French biological tradition. Nevertheless, one point did link Monod to French history: his fruitful interactions with André Lwoff. As we shall see, these interactions were necessary for the development of Monod's science, both technically and intellectually speaking.

KEYWORDS - Jacques Monod, enzymatic adaptation, bacterial growth, André Lwoff, French neo-Lamarckism.

Introduction

In 1947, Monod wrote a synthetic report on enzymatic adaptation, a phenomenon which had begun to arouse the interest of biologists (especially embryologists and geneticists). In this long paper (66 pages), Monod discussed the importance of the phenomenon in twentieth cen-

tury biology, the experimental results already obtained and, most importantly, presented a quite detailed model in order to explain how enzymes could be so well adapted to the nature of the substrate (Monod 1947). During the next 13 years, until the publication of the classical paper setting out the operon model (Jacob and Monod 1961), Monod patiently deconstructed all the hypotheses he had introduced in this first attempt to produce a general explanation in terms of the interactions of molecules (Morange 1994, 196-198). This crucial aspect of Monod's research during the 1950s was emphasized by Michel Morange; it led him to propose that "Monod never discovered what he expected" (Morange 2010b, 77).

The aim of the present paper is to recount some stages of the first part of the history of the biological problem of enzymatic adaptation, in order to observe how Monod tried to break from the legacy of traditional French biology and its deeply entrenched Lamarckian atmosphere. I will first begin with an overview of the discovery and first interpretation of the phenomenon in the Pasteur Institute at the end of the nineteenth century and the very beginning of the twentieth. I will then examine how Monod developed his first hypotheses during the 1940s up to his 1947 model. These hypotheses were developed in opposition to traditional French biology, since Monod was convinced of the importance of quantitative methods and classical genetics in the attempt to construct real scientific knowledge concerning vital phenomena, that is, to construct a non-teleological science.

In the last part of the paper, however, I will emphasize a point that links Monod to French history: his fruitful interactions with André Lwoff. It is well known that Monod was always reluctant to be considered as a follower only – and obviously he was not just that. Nevertheless, this is precisely why it is historically important to understand that Lwoff exercised a real influence on him during the 1930s and the 1940s.

In this paper, I will only focus on Monod's work from 1933 to 1947. This limitation has two reasons. The first is that the next period of Monod's researches, from his collaboration with Melvin Cohn in the early 1950s to his involvement in what would become the operon model with François Jacob, has already been very well documented (Jacob 1980; Grmek and Fantini 1982; Jacob 1987; Morange 1994, 194-212; Gaudillière 2002, 246-291). The second reason concerns the "Lysenko affair" and its direct impact on Monod's ways of thinking. In France, Lysenkoism really became a matter of concern in September 1948, when the journal *Combat* asked four scientists, including Monod, to analyze the scientific claims of Lysenko. Monod was deeply affected by what he perceived as an eruption of irrationality in science. The interactions

between the political commitment of Monod and the way he wanted to construct molecular biology during the 1950s are very complex, and their study would require an article of its own.[1]

The scientific characterization of enzymatic adaptation: the legacy of Duclaux, Diénert and French neo-Lamarckism

Most of the first studies on what would come to be called enzymatic adaptation were performed on microorganisms.[2] The first characterization of the phenomenon was achieved by Emile Duclaux during the late 1890s at the Pasteur Institute. Duclaux was at the beginning of his career a close associate of Louis Pasteur, and after the death of the latter (1895) he became the second director of the Institute (Morange 2010a). His most important publication was a monumental *Traité de microbiologie*, published in four volumes from 1898 to 1901 (seven volumes were initially planned). The second volume is entitled *Diastases* [i.e. enzymes]*, toxines et venins*, and the fifth chapter of this volume is devoted to the "causes that influence secretion of enzymes" (*causes qui influent sur la sécrétion des diastases*; Duclaux 1899, 83-93). In this chapter, Duclaux proposed the first clear discussion of the phenomenon of enzymatic adaptation.

During the 1890s, Duclaux studied the way cells produce enzymes depending on the composition of the medium. He obtained interesting results with two experimental systems: *Aspergillus glaucus* and *Penicillium glaucum* (both fungi). These organisms were relevant for this kind of research at the end of the nineteenth century because they secreted digestive enzymes into their environment. Duclaux studied the production of four enzymes by *Aspergillus*: lab-ferment, casease, saccharase and amylase. He clearly observed that saccharase was produced only in the presence of saccharose, and that both protease (lab-ferment and casease) were produced only when the medium contained milk.

At the beginning of the chapter, Duclaux raised the problem of the mode of secretion of enzymes by cells: Is it constant and independent of the medium or is it controlled by it? A few pages later, he was able to conclude:

[1] This particular aspect of Monod's work will be examined in more detail in a forthcoming work, which is developed by Richard Burian (Virginia Tech, United States), Jean Gayon (Université Paris-1, France) and myself.

[2] The phrase "enzymatic adaptation" was coined only in 1930 by Henning Karström in his doctoral dissertation. Nevertheless, in order to simplify the discussion I will use the phrase here to describe works performed before this date.

> To sum up, we see that, in the case of these two microscopic species [*Aspergillus g.* and *Penicillium g.*], the production of diastases depends on the manner of nutrition. This is the essential point of the question we posed.[3]

During the next months, similar results were found by several biologists in Europe (for example F.C. Went in Germany), confirming the reality of a hitherto unknown phenomenon. Duclaux decided that this discovery was important enough to become the topic of a doctoral dissertation. His student, Frédéric Diénert, performed many experiments on another experimental system, which was about to become the most used for the purpose. His work was devoted to the study of the enzyme galactozymase, which is produced by yeast (*S. cerevisiae*) in order to metabolize galactose. The results he obtained established that the ability to ferment galactose occurs exclusively in cells that have been grown on galactose, and that fermentation will start only after an induction period of a few hours. That means that yeasts have to get used to this sugar. The main problem was then to understand how this habituation process occurs:

> All these facts raise curious problems, when they are studied from the point of view of the production of the alcoholic enzyme. It is necessary that this enzyme exists and functions in some yeasts and not in others; that in the same yeast, it appears in some cases and not in others. (Diénert 1900a, 139-140)

In 1900, Diénert defended his PhD dissertation (*Sur la fermentation du galactose et sur l'accoutumance des levures à ce sucre*) and then proposed two kinds of mechanisms in order to explain enzymatic adaptation: (1) the galactose can directly transform the enzymes already present in the cell into galactozymase; (2) the galactose activates the production of a new enzyme, the galactozymase (Diénert 1900b, 67).

It is important to notice that these two general possibilities (transformation *versus* synthesis *de novo*) were maintained throughout the first part of the twentieth century, including in Monod's 1947 synthetic report. According to Diénert, the first hypothesis was more convincing, primarily because it appeared to be simpler. But Diénert also added a second argument, of some significance in the history of the concept of enzymatic adaptation. Just as Monod would do 40 years later, Diénert observed that fermentations of two different sugars (glucose and galactose, for example) were not independent. If one existed, it slowed the speed of the second. This result seemed to be understandable only if one assumed that the two substrates competed for the same molecule of enzyme, that is to say, if one enzyme was directly transformed into the other, and that indeed was the main conclusion of Diénert (1900b, 68).

[3] Duclaux (1899, 87). If not otherwise stated, translations are my own.

But Diénert also showed that this "acclimatization" can occur without any cell multiplication. Unadapted cells, suspended in a phosphate buffer without any external source of nitrogen, will adapt to galactose, provided galactose is present. For later biologists, including Monod (Monod 1947, 232), this result proved that selection was not involved, i.e. that enzymatic adaptation was a physiological and individual process. For Diénert, this precise phenomenon belonged to the general problematic of physiological acclimatization:

> According to our results, we have supposed that there is only one enzyme which can be transformed during the acclimatization, in order to attack the galactose. This change in the constitution of the enzyme comes with a change in the constitution of the protoplasm. Hence, the phenomenon of acclimatization is, in this case, a profound modification of the cell's state, caused by a sugar very close to glucose. (Diénert 1900b, 71)

Diénert's personal conclusions perfectly fit the general framework dominant in French thought at that time, based on the direct and adaptive action of the components of the environment on the morphology and physiology of plastic living things. Evolutionary change, it was thought, was only the gradual addition of physiological and individual variations by the general law of the inheritance of acquired characters (Loison 2010a). This adaptationist form of neo-Lamarckism structured French biology for nearly half a century (1880-1930).

One of the most orthodox representatives of this French neo-Lamarckism, the zoologist Frédéric Houssay, professor at the Sorbonne, considered an organism only as a "local and brief manifestation of an infinity of discrete actions, present or past, whose origin is foreign and lies outside of it" (Houssay 1920, 175). In his last but also primary book, *Force et cause*, published in 1920, Houssay developed the idea of an all-mighty environment, able to transform actively the chemistry of the organism; and, as evidence, he referred to the phenomenon of enzymatic adaptation:

> If we think that all steps in digestion involve enzymatic actions, that all the enzymes of each living thing are rigorously *adapted* to the nature of its usual food, that we can alter the enzymes, in quality and quantity, by cautiously changing the food, and then a congruence has been established between the chemistry of the living thing and the chemistry of what feeds it. (Houssay 1920, 178; my emphasis)

This text is important because, for the first time – at least in French biology – the word "adapted" was used to indicate the appropriateness between the nature of the substrate and the nature of the enzyme. As this happened in a Lamarckian context, it was impossible not to understand what this kind of adaptation referred to.

Emile Duclaux himself was one of the most explicit Lamarckians at the Pasteur Institute. A few years before Duclaux started working on enzymatic adaptation, during the 1880s, Pasteur and his associates studied the dependence of virulence in microbes on the medium in which they were grown. They showed that this physiological characteristic could be hereditarily transformed by using successively different types of media. Duclaux was convinced that these results were the first experimental evidence of the reality of the inheritance of acquired characteristics (Duclaux 1898, 257). More generally, he believed that the diversity and evolution of microorganisms was the consequence of the "plasticity of the protoplasm" because the direct action of the environment on cells enabled them to adapt themselves physiologically and to transfer this adaptation by inheritance (Duclaux 1898, 605).

When Jacques Monod came to Paris at the end of the 1920s, in order to start studying biology, this adaptationist Lamarckism was still alive, at least in the old Sorbonne. During the period from 1910 to 1930, however, the reality of soft inheritance was strongly challenged. That is one of the reasons why another version of Lamarckism – much more finalistic than the previous one – was about to be developed by scientists like Albert Vandel, and especially Pierre-Paul Grassé (Loison 2011). From the early 1940s, the atmosphere of French general biology became strongly spiritualist, vitalist, and finalistic, as the famous book by Henri Bergson, *L'Evolution créatrice*, first published in 1907, was an explicit reference, even for scientists. This specific context must be kept in mind in order to fully understand why Monod was so concerned about clearing biology of finalism, and why he wanted to develop unusual methods (from the French point of view) in order to produce biological knowledge.

The three roots of Monod's first model (1947)

The legacy of biometry: Monod and the measuring of bacterial growth

In 1941, Monod defended a doctoral dissertation devoted to the study of bacterial growth (Monod 1942). Reading this text will convince anyone of the extreme aptitude of Monod both for hypothetico-deductive arguments and for measuring and quantification. The entire dissertation is full of graphs and curves. As Richard Burian and Jean Gayon have already pointed out, this way of making science was typical of Monod's style, quite different from the style of classical French zoology then prevalent (Burian and Gayon 1999, 328).

Eight years before, in 1933, Monod had published the first articles of which he was the sole author (in 1931 he had been the co-author of two papers on the morphology of ciliates, with Edouard Chatton, as well as André and Marguerite Lwoff). These 1933 papers were devoted to the study of "galvanotropism" among ciliates (oriented movement in response to an electric stimulus) and already showed Monod's taste for quantitative research. The complete title of one of these texts is "Données quantitatives sur le galvanotropisme des infusoires ciliés" (Quantitative findings on galvanotropism in ciliate infusorians; Monod 1933). Thirty-two years later, at the end of his career, when Monod received the Nobel Prize with François Jacob and André Lwoff, he acknowledged debts to only very few people, and one of them was his brother-in-law, Georges Teissier (Monod 1966). Teissier is a remarkable figure in the modern history of French biology, both because he was a brilliant population geneticist (Gayon and Veuille 2001), and because he was persuaded of the fundamental importance of biometry for the task of developing biology as a real science. Note that the term "biometry," here and throughout my paper, is understood in its general sense (like Teissier and Monod did), i.e. the use of quantitative methods for the study of living phenomena, and does not refer to the school of biometricians connected to Karl Pearson in the debates with William Bateson.

Moreover, some of Teissier's works directly concern the problem of growth, and he developed mathematical tools on that subject (Teissier 1936), tools which were used later by Monod. During the late 1930s, Teissier and Monod regularly discussed these topics (Monod 1942, 3), and in 1936 they even published together a brief paper in the *Comptes rendus de l'Académie des sciences* concerning the growth of ciliate cultures (Monod and Teissier 1936). According to Monod himself, the influence of Tessier was decisive and persuaded him of the necessity of quantitative studies (Monod 1966, 475; Lwoff 1980, 2).

The first attempt to apply this method was made on the galvanotropism of ciliates, as mentioned before. Since the end of the nineteenth century, ciliates were involved in several different research programs all around Europe and the United States (Richmond 1989; Schloegel and Schmidgen 2002; Morange 2006). For various reasons, they were seen as the best "model organisms" to explore, on an experimental basis, some of the most important issues of general biology such as sexuality (see the third section of the present paper) or heredity.

Monod was soon convinced that the results he obtained on galvanotropism could be interpreted as indicators of the physiological age of the cells. He then faced another problem. How could the age of microorganisms, which can divide themselves indefinitely, be defined? In order to an-

swer this new question, in 1935 Monod started studying the growth of ciliate cultures (Monod 1935). But he quickly ran up against practical problems, as we will see in the last part of this text, and he subsequently changed his experimental system from ciliates to bacteria. In 1937, he published his first article on what would become his exclusive research program for the next ten years: the growth of bacterial cultures and its enzymatic components (Monod 1937).

Despite the disaster of 1940, that is, the collapse of the entire country because of the Nazis invasion, Monod, who was still working in Paris, managed to perform many experiments on the kinetics of bacterial growth, with the intention of completing his doctoral work as quickly as possible. At the end of 1940, Monod obtained surprising results:

> From the first experiment on, I noticed that, whereas the growth was kinetically normal in the presence of certain mixtures (that is, it exhibited a single exponential phase), two complete growth cycles could be observed in other carbohydrate mixtures, these cycles consisting of two exponential phases separated by a complete cessation of growth. (Monod 1966, 475)

Monod rediscovered the phenomenon that, in 1900, Diénert had already observed in yeasts: the presence of some specific sugars (glucose, fructose, saccharose, mannite, manose) inhibits the fermentation of other sugars by the bacterium (Diénert named it the "glucose effect"). That is why the growth of bacteria has two phases if the only sources of carbon are carbohydrates: during the first, only the glucose is metabolized, during the second, after a few hours, the second carbohydrate allows the growth to continue (Figure 1). Monod obtained characteristic graphs of this phenomenon and published them for the first time in May 1941 (Monod 1941). In his doctoral dissertation, Monod coined the term "diauxie" (i.e. double growth) to refer to this physiological process in order to insist both on its novelty – which required a new vocabulary – and on the typical double growth phenomenon shown by graphs (Monod 1942, 139).

As early as 1941, Monod interpreted the cessation of growth as an induction period which is necessary for the adaptation of bacterial enzymes to the new substrate. What has to be emphasized is the way Monod finally met the problem of enzymatic adaptation. Monod is often described – including by himself – as a biochemist, and for sure, since December 1940 and the surprising results he obtained, he attempted to become one. His very first works, however, were not devoted to biochemistry but to the biological characteristics of ciliates, which, ultimately, led him to enzymatic adaptation. The common problematic of the experiments he performed during the 1933-1942 period was not that of a biochemist, but of a biometrician: Monod was deeply convinced that biology needed quantitative

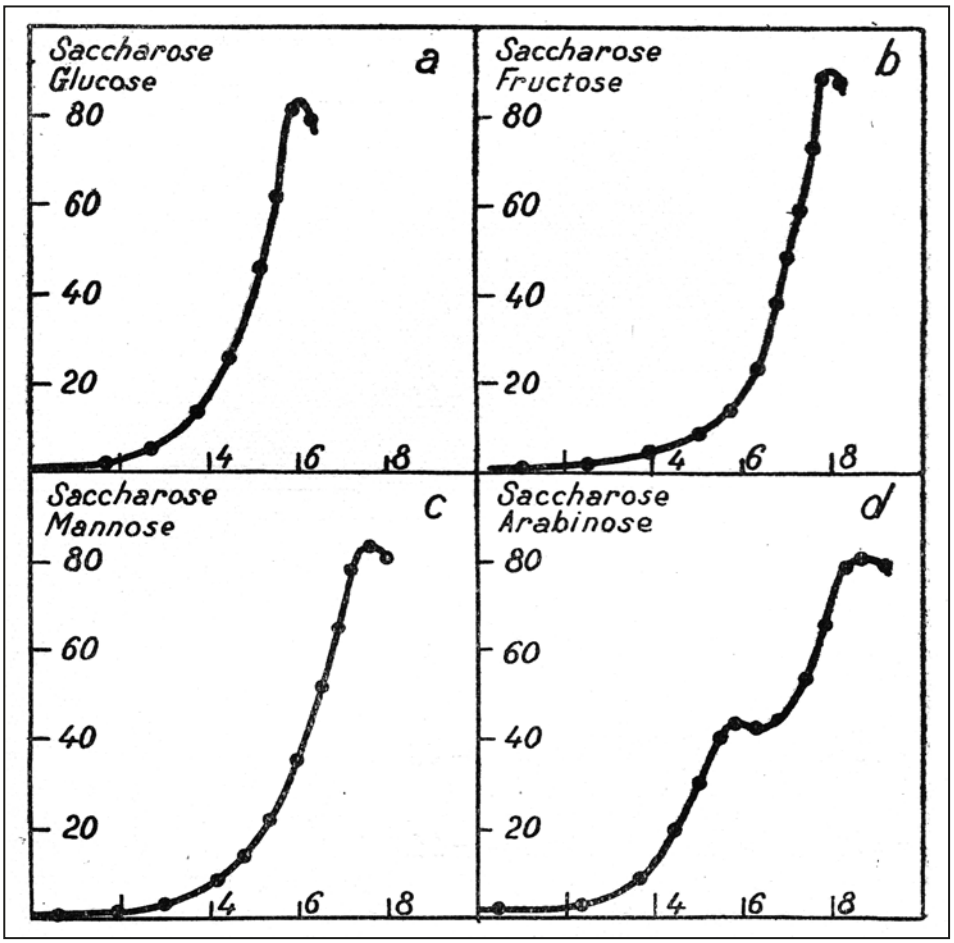

Fig. 1 - Graphs showing growth curves of *Bacillus subtilis* in the presence of different carbohydrate pairs serving as the only source of carbon in a synthetic medium (from Monod 1942). These graphs represent some of the numerous results of Monod on the phenomenon of diauxie and show that in the four cases studied here a diauxic growth only occurs with the mixture of saccharose and arabinose (d).

studies at the population level in order to escape from the old tradition of morphological description.

As Jan Sapp has insisted, the "remarkably descriptive character of French biology" (Sapp 1987, 129) was reinforced at the Sorbonne during the 1920s and the 1930s because of the failure of the first Neo-Lamarckian program (Loison 2011). It is important to emphasize that the official – and very distant – *maître* of Monod during his PhD work, the embryologist Charles Pérez, director of the laboratory of zoology at the Sorbonne, belonged to this tradition of descriptive morphological zoology.

Hence, it was because of methodological issues that Monod became interested in bacterial enzymes, and then, only as a consequence, in biochemistry. Note that during the 1930s, in Paris, Philippe L'Héritier and Georges Teissier performed the first population genetics experiments based on the study of population dynamics of *Drosophila* in "démomètres," i.e. population cages that had been invented by L'Héritier in 1932. Their purpose was at first purely biometrical. They wanted to study the demography of different populations of flies in a given milieu (Gayon and Veuille 2001, 79-80). This is exactly the kind of methodology Monod chose to apply to his first work on the growth of unicellular organisms. During the early 1950s, Monod even conceived an experimental equipment, the *bactogène*, in order to stabilize the different parameters of culture, such as temperature, amount of carbon sources, etc. It is not irrelevant to see this equipement as a kind of population cage designed for bacterial cultures, and hence as further evidence for the importance of French biometry for Monod.

It is well known that Monod became fascinated by the experimental possibilities allowed by the exponential phase of growth of bacterial cultures (Monod 1942, 16-17). He liked to compare such a system to a perfect gas. Individual peculiarities did not matter, and only population characteristics were relevant in order to establish scientific laws of nature. Through a new quantitative approach, Monod's ultimate goal was indeed to physicalize biology (Judson 1996, 348).

The legacy of immunology: Monod and the mechanism of enzymatic adaptation

The first part of Monod's 1942 book *Recherches sur la croissance des cultures bactériennes* concerns general issues about bacterial growth: methodological principles, determination of constants of growth in the presence of different carbohydrates, etc. Highly interested by the unexpected results he had obtained since December 1940, Monod decided to devote the entire second part to the specific study of diauxie. After discussion of numerous detailed results of bacterial growth on different combinations of sugars, he ended his text with a discussion of the explanation of diauxie.

For Monod, there was no doubt that this new phenomenon was linked to enzymatic adaptation. The other logical possibility, the selection by the medium of bacterial mutants, was quickly disproved (Monod 1942, 175). Monod then referred to the classical work of Henning Karström (1930), and proposed that the carbohydrates that are first metabolized were attacked by "constitutive" enzymes and that the second ones were

attacked by "adaptive" enzymes, i.e. enzymes that are not already present in the cytoplasm of bacteria (Monod 1942, 186). If this hypothesis is true, diauxie can be explained by the inhibition of the adaptation process as long as the first sugar is present in the medium and metabolized by the cell. Hence, the problem was to understand the molecular mechanism of such an inhibition.

Before the late 1930s, the precise explanation of enzyme adaptation was not really discussed, that is to say, no detailed mechanistic model was proposed. Above all, Monod was disappointed by the fact that "purely teleological explanations prevailed" (Monod 1947, 246-247). Cells were supposed to perform only the chemical reactions they "need" (even in Karström's hypothesis). To him, this kind of explanation belonged to a pre-scientific stage of biology, when the life sciences, unlike physics, had not yet assimilated the "postulate of objectivity" (Monod 1971, 21-22).

In 1938, the English biochemist John Yudkin proposed a detailed scheme in order to biochemically explain enzymatic adaptation. This general explanation was called the "mass action" theory (Yudkin 1938). Yudkin's work was developed under the supervision of Majory Stephenson at Cambridge, which was at that time the leading laboratory for the study of bacterial metabolism in general, and, since the early 1930s, the question of enzymatic adaptation in particular. Yudkin's model was based on the hypothesis that enzymes have common precursors in the cell, which can be transformed into active molecules depending on the presence of different substrates. In this model, however, the substrate was not inducing the adaptation because the chemical transformations of the precursor happened all the time. As an alternative hypothesis, Yudkin proposed that the velocity constants of the reactions were different: that of the reaction producing the constitutive enzyme was supposed to be far higher than that of the reaction producing the adaptive one. This implied that the effective formation of the adaptive enzyme could only occur when both the first sugar had been completely consumed and the second was present in the medium. This model provided a very satisfactory explanation, and was developed for almost twenty years by Yudkin and his associates (such as Joel Mandelstam; see Mandelstam 1952).

In 1942, Monod believed that Yudkin's hypothesis was at least probable (Monod 1942, 196). But if Yudkin was right, the rate of enzyme formation should decrease continuously with time, because the concentration of substrate is maximal at the beginning of the adaptive process. What was observed was more or less the contrary: the initial period of adaptation was characterized by a rising rate of enzyme formation, which fell off after some time to give an S-shaped curve. That is why the American microbiologist Sol Spiegelman proposed another model in which the

adaptive enzyme is endowed with self-duplicating properties. This kind of autocatalytic mode of formation perfectly explained the S-shaped curve of enzyme synthesis (Gaudillière 1992). This model was derived from the general hypothesis of "plasmagenes," that is cytoplasmic units which were thought to be able to genetically reproduce themselves without any relation to the nucleus (Sapp 1987).

It is important to note that Monod was never convinced by Spiegelman's model. At the end of June and beginning of July 1948, André Lwoff – with the support of the CNRS and of the Rockefeller Foundation – organized in Paris an international meeting devoted to the theme "Biological Units Endowed with Genetic Continuity." This meeting gathered biologists of prime importance, some of whom were about to play a major role in the setting-up of molecular biology. Most of them were at least interested in the possibilities offered by conceptions that were not part of classical Mendelian knowledge. The only exception was Monod. In his contribution, entitled "Facteurs génétiques et facteurs chimiques spécifiques dans la synthèse des enzymes bactériens", he strongly opposed Spiegelman's hypothesis and the whole theory of plasmagenes in general, and he did so on the grounds that they were in opposition with "Mendelian heredity, which still constitutes the general – if not absolute – rule" (Monod 1949, 196). To Monod, the plasmagene theory seemed too close to Lamarckian soft inheritance. As Jean-Paul Gaudillière has already noticed (Gaudillière 1991, 55), this intransigent opposition must have been motivated by the determination of Monod to exclude for good Lamarckism from modern biology because such ways of thought always reintroduce finalism in science. From the very beginning, Monod wanted to construct a non-teleological mechanism explaining adaptation at the molecular level.

From 1942 to 1945, for complex and sometimes unclear reasons, Monod progressively lost his confidence in the "mass action" theory of Yudkin. In 1943, he performed a set of experiments on the influence of the concentration of the substrates on the speed of adaptation. Monod showed that the speed of adaptation is not a function of the degree of saturation of the enzyme by the substrate, as predicted by Yudkin's model (Monod 1943). That is why he proposed that the substrate plays an active and direct role in the formation of the adaptive enzyme, by modelling a precursor. From Yudkin, he adopted the idea that different enzymes have the same precursor, because this hypothesis offered a good explanation of competitive interactions between different specific enzyme-forming systems (Monod 1944). Monod was now looking for a way to understand how the substrate could mechanically drive the adaptation process.

Gaudillière has shown how Monod very quickly became interested in the model the immunologists had constructed in order to explain

antibody formation (Gaudillière 1992). In 1940, Linus Pauling had proposed that the geometry of the antigen molecule directly determines the structure of the antibody and its high specificity. As early as 1945, Monod tried to draw an analogy between antibodies and adaptive enzymes: both molecules could be formed "under the direct modeling influence" (Monod 1945, 40) of antigens or substrates. This analogy was quite common outside French biology, and widely discussed. For example, in the second edition of his book *The Production of Antibodies* (1949), the Australian immunologist and virologist Frank Macfarlane Burnet developed it, and then referred explicitly to Monod's 1947 model (Burnet and Fenner 1949, 93). Nevertheless, most of the scientists who were discussing the possibility of a common mechanism were reluctant to press the idea too closely (Burnet and Fenner 1949, 95). Monod appeared to be more extreme, and because of his obsession with unification he was convinced of the high scientific value and indeed also of the logical necessity of general and unified models. That is why he tried to maintain this analogy as late as 1958, even though several experimental facts were already opposed to it (Gaudillière 1991, 58).

In his 1947 report Monod proposed, for the first time, a detailed scheme of the mechanism of enzyme formation (see Figure 3). He supposed that the enzyme was a "complex structure, which would be created through 'polymerisation' involving, besides the specific 'B' units, non-specific ('i' units) building blocks, which might be common to many or all enzymes or protein molecules" (Monod 1947, 276). The role of the substrate, its effective modelling effect, was to stabilize the whole structure. Another hypothesis was that the presence of enzymes increased the probability of favourable arrangements between "B" and "i" units, and further favoured the formation of aggregates of similar structure. This could account, according to Monod, for the autocatalytic formation of enzymes that Spiegelman opposed to Yudkin's model. But this hypothesis could also reintroduce the self-duplicating conception. Hence, it was necessary for Monod to link his model with classical Mendelian genetics.

The legacy of classical genetics: Monod and the ambiguous role of the gene in enzymatic adaptation

In 1936, Monod went to America with Boris Ephrussi who had persuaded him to come to Morgan's laboratory at Caltech. It is well known that the young biologist did not get as involved in experimental work as Ephrussi had expected during this stay (Judson 1996, 351). Nevertheless, the discovery of what might be called "genetics in the making" highly impressed Monod. This is how he should later recall this episode:

> But under the influence of another friend whom I admired, Boris Ephrussi, I was equally tempted by genetics. Thanks to him and to the Rockefeller Foundation, I had had an opportunity some years previously to visit Morgan's laboratory at the California Institute of Technology. This was a revelation for me – a revelation of genetics, at that time practically unknown in France; a revelation of what a group of scientists could be like when engaged in creative activity and sharing in a constant exchange of ideas, bold speculations, and strong criticisms. […] Upon my return to France, I had again taken up the study of bacterial growth. But my mind remained full of the concepts of genetics and I was confident of its ability to analyze and convinced that one day these ideas would be applied to bacteria. (Monod 1966, 476)

Not only had Monod discovered a new and stimulating way of making science – absolutely opposed to that of the Sorbonne – but he also admired how genetics, the first formal discipline in biology, could bring clarity and exactness to the life sciences. Even if Monod was never a geneticist, he kept in mind the importance of genes in order to establish a complete explanation of the fundamental properties of living things (Judson 1996, 352). In Monod's mind it was obvious that the fight against both finalism and Lamarckism was inseparable from the total acceptance of classical genetics, and this inclination remained constant in his later writings.

Monod had so far explained the adaptation process only at the level of the enzyme without any consideration of the possible effects of the regulation of gene activity. But by 1947, he was forced to introduce a genetic component into his model. If he had not done so, his explanation could have been seen as a variation only of that which Spiegelman had already proposed, implying that molecules can be formed and inherited without any relations to genes. Such considerations left too much room for the possibility of a kind of inheritance of acquired characteristics.

Besides this more or less metaphysical positioning, Monod also had experimental arguments. In 1946, with his associate Alice Audureau, he studied ML-strains of *Escherichia coli-mutabile* (isolated from André Lwoff's intestinal tract). These bacteria were originally "lactose-negative" organisms, which is to say that they were unable to grow on media where the only source of carbon was lactose. Monod and Audureau showed that a mutation was allowing these bacteria to become "lactose positive."

The most interesting thing was that the new *lac*$^+$ bacteria were able to produce the appropriate enzyme after both the exhaustion of glucose in the medium and a necessary inducing period: their growth curves were typical of the phenomenon of diauxie (Figure 2), implying that the enzyme involved was an adaptive one (Monod and Audureau 1946).

This case appeared to belong with classical genetic mutations because the transformations observed were stable through generations, rare (the rate was about 10^{-5}), and spontaneous (not depending on the quality of

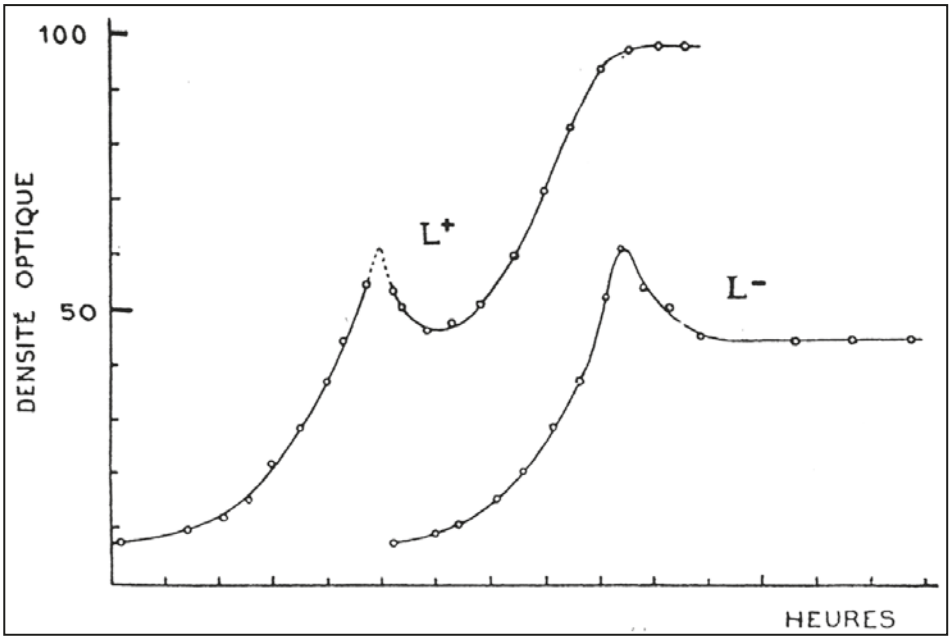

Fig. 2 - Graph showing typical diauxic curves obtained after mutation of *E. coli*. (From Monod and Audureau 1946) These results implied that enzymatic adaptation had a genetic basis.

the medium, i.e. the presence of lactose). Contrary to classical mutations, however, "the original strain (*lac*$^-$) and the mutant strain (*lac*$^+$) did not differ from each other by the presence of a specific enzyme system, but rather by the ability to produce this system in the presence of lactose" (Monod 1966, 475). This implied necessarily that the whole process of enzymatic adaptation had a genetic basis, in other words, that it was "a truly genetic property" (Monod 1966, 476).

Because Monod was convinced that adaptation occurred only at the level of the enzyme at that time, his ideas of the exact role of the gene in the 1947 model were quite complex. Yet, this role must have been important in Monod's mind, because he explicitly named his model the "general conception of gene-controlled, substrate-induced enzyme formation" (Monod 1947, 271). As we just saw, Monod believed that the specific structure of the enzyme, which allows it to metabolize a particular substrate, was the result of a modelling process of different sub-units by the substrate itself. Nevertheless, he was also convinced of the importance of the work of Beadle and Tatum on *Neurospora*, work that had accumulated evidence about "one gene – one enzyme" relations (Monod 1947, 272; Gaudillière 2002, 258). Monod tried to put together the mechanism

of a modelling process and the "one gene – one enzyme" axiom in a unified explanation (Figure 3).

By doing this, he also wanted to make his contribution to the development of physiological genetics, which appeared at that time to hold a promising future for genetical research. It must be recalled, here, that physiological genetics had already been developed during the late 1930s in France, by Boris Ephrussi, who had carried out a research program based on the transplantation of eye disks of *Drosophila*-larvae in collaboration with George Beadle (Sapp 1987, 132-134). According to Monod's 1947 model, the specific activity of an enzyme (adaptive or not) must belong to some restricted areas of its structure. The gene involved in the synthesis of a particular adaptive enzyme would then "manufacture the 'specific building blocks' required to form those specific active sites of the enzyme" (Monod 1947, 276).

Monod's scheme appeared more complicated and motley than that of Yudkin and Spiegelman because it linked classical and rigid gene control with induced adaptation at the protein level. The necessity of the genetic

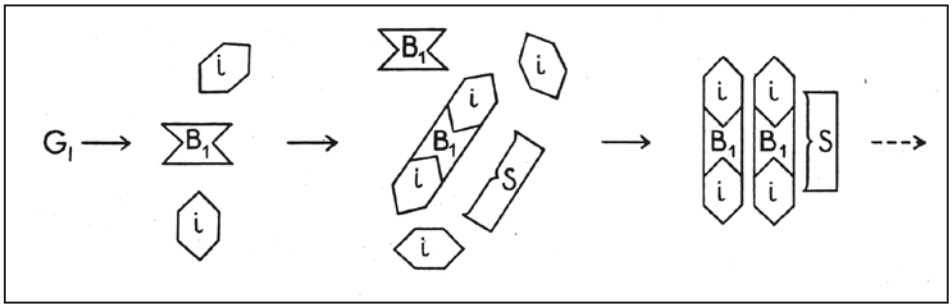

Fig. 3 - Drawing illustrating Monod's general model of gene controlled, autocatalytic enzyme synthesis. (From Monod 1947) - G_1: gene controlling the synthesis of the specific building blocks B_1; B_1: specific building blocks forming most of the active site of the enzyme; i: non-specific building blocks (common to several different enzymes); S: substrate.

component of the general explanation was motivated both empirically (results obtained in 1946 with A. Audureau) and metaphysically (opposition to any conception – such as Spiegelman's plasmagenes – that could reintroduce Lamarckism into modern biology). The last paragraph Monod devoted to the working of his model is explicit about the need to avoid any opposition to Mendelian genetics:

> This little scheme should not be considered as anything more than an attempt to show that substrate-induced, *autocatalytic*, competitive, enzyme formation can

> be understood without abandoning the concept of strict, continuous gene control. It may prove useful if it is confirmed that the process of enzyme synthesis is actually *inherently* autocatalytic, although essentially conditioned by the presence of a single gene, in each case. (Monod 1947, 277; emphasis in the original)

It was clear to Monod that one should not explain the phenomenon of enzymatic adaptation on the basis of hypothetic self-duplicating units such as plasmagenes, as Spiegelman had done. As he insisted a few lines before the cited passage, the "enzyme formed according to this scheme would *not* be a self-duplicating unit" (Monod 1947, 277; emphasis in the original). This case of auto-induction was indeed the result of complex interactions between different kinds of molecules, and the gene remained the only one able to have self-duplicating properties, and then could be the only bearer of heredity.

From 1940 to 1947, Monod pursued the objective of producing a non-Lamarckian and non-finalistic explanation of one of the most obvious cases of adaptation, that which occurs at the level of enzymes. To achieve his goal, he consciously tried to develop ways of thinking that were not usually privileged in French biology during the inter-war period, such as those of biometry and genetics. Nevertheless, Monod's early research programs, first on ciliates and afterwards on bacteria, were ramifications of Pasteurian microbiology too. Most specifically, in many senses, Monod's work was also indebted to André Lwoff.

The importance of André Lwoff: the implicit reintroduction of some Pasteurian biology

Like most of the young Parisian biologists of the first half of the twentieth century, Monod's initiation to real science did not happen in the Sorbonne, but during training periods in the marine station of Roscoff (Brittany). Here, he met many interesting people like Teissier, Lwoff, Ephrussi and Louis Rapkine, and, as a student, was able to observe what was science in the making. One of the dominant scientists in Roscoff during the 1920s and the 1930s was the protozoologist Edouard Chatton, the first *maître* of Lwoff. In close collaboration, Chatton and Lwoff developed microbiological techniques in order to cultivate ciliates in pure media, i.e., synthetic cultural conditions without any other microorganisms like bacteria. The will to experimentally control the physicochemical environment of living things was a typical legacy of nineteenth century French biology, and the works of Chatton and Lwoff continued this Bernardian-Pasteurian tradition (for a comprehensive study of the

importance of "purity" in biological practices around 1900, see Bonneuil 2008; see also Müller-Wille and Rheinberger 2012, 132-137). For protozoologists, this possibility of control was at that time decisive for the ability to understand some of the most important features of the physiology of these microorganisms.

One of these features was the determinism of the process of conjugation, a mode of sexuality without reproduction that is specific to ciliates. During the 1880s, the French zoologist Emile Maupas performed a set of experiments that definitively established the precise nuclear nature of this phenomenon (Maupas 1889). In opposition to August Weismann, Maupas believed that unicellular organisms were not immortal but, after a certain number of divisions, progressively declined if conjugation did not occur (Lustig 2000). As Rheinberger has pointed out, the results of Maupas' experiments "indicated that these organisms deteriorated when they were prevented from reproducing sexually and forced to reproduce by division alone over a certain number of generations" (Rheinberger 2010, 84). The primary function of sexuality was then to revive the physiology of the cell, and conjugation would hence be driven by internal causes (the age of the ciliates). During the late 1910s, the German protozoologist Max Hartmann challenged this conclusion. He cultivated organisms of the species *Eudorina elegans* (green algae) in an agamic way for an unlimited number of generations. To him, such results were decisive proof that fertilization was unnecessary for survival, whereas cellular division was. Following the general ideas of his teacher, Richard Hertwig, he was convinced that mitotic cellular division was responsible for a kind of "propagatory rejuvenation" (Rheinberger 2010, 90-91).

In 1923, for the very first time, Lwoff succeeded in cultivating a ciliate (*Glaucoma piriformis)* in a pure medium (Lwoff 1923). From 1923 to 1931, Chatton decided to examine Maupas's conclusions in light of the technical possibilities this opened up. He strongly opposed Maupas by showing that the quality of the medium – an external cause – could activate the conjugation process (Chatton and Chatton 1923). In September 1930 Monod went to Strasbourg to spend a year in Chatton's laboratory. There, he was able to learn classical techniques of Pasteurian microbiology, including the one developed by Lwoff and Chatton for cultivating ciliates in a pure medium. Chatton's teaching was decisive in Monod's formation because it allowed him to start his research program on the growth of ciliates, which finally led him, as we have seen, to enzymatic adaptation. Lwoff was always very disappointed that Monod never acknowledged his debt to Chatton, and thus, in a sense, to the legacy of French Pasteurian microbiology (Lwoff 1980, 2).

During the next few years, even if they were not in regular contact,

Lwoff was very influential on the way Monod developed his work on the growth of cell cultures. From 1935 to 1937, Monod worked on *G. piriformis*, because Lwoff showed that it was possible to cultivate this species on synthetic media and then it seemed conceivable to control different factors (like the concentration of the carbon sources) that determine the speed of the growth. Nevertheless, the case of *G. piriformis* was more or less an exception among ciliates; such synthetic cultures were impossible in most other ciliates. Moreover, such experiments required very complex types of media because the precise needs of *G. piriformis* were not known. Hence it was very difficult to develop any research program on the factors controlling the growth of this species. In 1937, Lwoff tried to convince Monod to change his experimental system and to switch from ciliates to bacteria, like *Escherichia coli*. It is well known that Monod was worried about the pathogenicity of such material, but finally accepted Lwoff's suggestion (Lwoff 1980, 3-4).

It is also well known that Lwoff was the first to interpret correctly the surprising results that Monod obtained in the last days of December 1940 (Lwoff 1980, 4). Michel Morange has emphasized that, because of his huge biological learning – especially his knowledge of French general biology – Lwoff was able to understand that the phenomenon of diauxie was a consequence of the involvement of adaptive enzymes, and hence propelled Monod to begin working in the right direction (Morange 2005, 593). In December 1940, it was still Lwoff who gave to Monod the appropriate literature concerning enzymatic adaptation, including the classical book of Marjory Stephenson, *Bacterial Metabolism*, and Karström's doctoral dissertation (Lwoff 1980, 4).

Monod completed his doctoral dissertation in 1941, a work that obviously did not interest the old Sorbonne and its tradition of morphological description (Lwoff 1980, 4; Jacob 1987, 254-255). Lwoff appeared to be the only one to hold a high opinion of the importance of Monod's early work, and he recruited him as soon as possible, in the autumn of 1945 (Judson 1996, 361), just after the end of the war. Jean-Paul Gaudillière has shown that at this time, when Monod became an official member of the "grenier" (attic; Lwoff's laboratory), he learned directly from Lwoff some microbiological methods of selection of biochemical mutants that were useful for the study of diauxie (Gaudillière 2002, 253).

Lwoff, in his old age, liked to say that his most important discovery was François Jacob. What is true for Jacob could also be true for Monod; without these fundamental interactions – which link Monod to French general biology – the scientific trajectory of Monod would have been very different. The significance of Lwoff's role is even more obvious in the later unification of the works of Jacob on lysogeny and of Monod on

enzymatic adaptation; but this happened after 1947, so I will not develop this point here. It is indeed possible to produce another example of the influence of Lwoff upon Monod just by turning back to the 1947 report entirely devoted to the question of enzymatic adaptation. Despite the fact that this text dealt with a topic on which Lwoff never had worked himself, it shows very convincingly how deep the influence of Lwoff's ideas on his young colleague really was.

During the 1940s, enzymatic adaptation began to interest many biologists, both because it could be a model in the explanation of the way specific molecules are produced, and because it could help to fill the gap between genetics and embryology. It became more and more pressing, indeed, to understand how cells with identical genomes may become phenotypically differentiated by producing different active molecules. Monod was of course aware of this potential of enzymatic adaptation for a more general model of ontogeny. In his 1947 text, the last section is explicitly devoted to this question ("Adaptive enzymes and cellular differentiation"), and in the general introduction, Monod discussed "whether the established facts concerning substrate-induced enzyme synthesis as it occurs among microorganisms may help in understanding the processes of gene action and cellular differentiation" (Monod 1947, 225).

What is surprising is not that Monod discussed this question at all, but rather the way in which he addressed it. According to him, embryological development requires permanent modifications of the cell's potentialities. On the other hand, enzymatic adaptation seemed to be involved only in "modulations," that is changes "in the properties of a cell, occurring under an external influence, involving no irreversible modification in the *potentialities* of the cell" (Monod 1947, 279; emphasis in the original). Monod was forced to notice that "there is not a single authenticated case of true *substrate induced* specific enzyme formation resulting in a *permanent* modification of the cell's potentialities" (Monod 1947, 282; emphasis in the original). Hence, it appeared that enzymatic adaptation in itself could not play a direct and important role in irreversible differentiation and, subsequently, in embryological development.

Given that enzymatic adaptation seemed not relevant to understanding cellular differentiation, Monod could have stopped the discussion at this point; but he decided to continue, and in the last three pages of his text, he proposed a rather different mechanism of ontogeny. Firstly, he hypothesized that embryological differentiation may occur only after many cell divisions, when the organism already comprises thousands of cells. At this point, the number of cells was large enough to allow the efficiency of a classical mutation/selection process. In 1947, it was clear to Monod that only genetic mutations had the stability required to produce

truly permanent and irreversible differentiations. That is why he wanted to explain ontogeny in the same way as Darwinians explain phylogeny. Nevertheless, one major problem remained: what kind of mutation could confer a selective advantage during embryological development? Monod proposed the following answer:

> It is possible, in principle, at least, that certain types of mutations might – under certain specific conditions – confer a strong selective advantage upon the cell carrying it, while being almost lethal under any other conditions. In particular, this might be the case of mutations involving losses of functions. (Monod 1947, 285)

"Losses of functions" have to be understood at the metabolic level, and may be advantageous in certain stages of ontogenesis because the non-performance of biosynthetic reactions must lead to an economy of energy for the cell. This was precisely the theory which André Lwoff had patiently developed from 1932 to 1943 (Loison 2012), and Monod explicitly referred to him (Monod 1947, 285). For Lwoff, physiological evolution during phylogeny must be seen as going through successive losses of function, at least for unicellular organisms like protozoa and bacteria. Metabolic complexity was supposed to be maximal at the beginning and then decreased progressively (Lwoff 1944). Lwoff's theory was grounded on a very typical idea of the last third of the nineteenth century: because of the second principle of thermodynamics – the general rise of entropy in the physical universe –, it was thought that biological evolution, after an explosive start, had fallen off and could even stop and then generate extinction (Loison 2010b). Lwoff's own conception was explicitly linked to such considerations, and hence belongs to the legacy of a general biology of the kind that Burian and Gayon have proposed (Burian and Gayon 1991).

Monod took Lwoff's general idea, and applied it to the particular case of embryological development: physiological and morphological differentiation during ontogeny must be the result of successive losses of function under selective pressure. Even if, as far as I know, Monod never again used this specific explanation, these last pages of the 1947 report are important because they show the direct influence that Lwoff must have exercised on his young colleague. Monod was of course too proud to recognize anyone as his master but he was nonetheless aware of his debt to Lwoff. He explicitly recognized this debt on two prestigious occasions: during his Nobel Lecture, in 1965 (Monod 1966), and at the beginning of his Inaugural Lesson when he entered the *Collège de France* on 3rd November, 1967:

> I express to you my gratitude, without, however, being able to hide from myself or from you, that others had acquired, well before me, more claims to such a big honour. It is of André Lwoff that I think, whose example I was only trying to follow; I learnt at his side how the most trenchant criticism can yet be generous, and that extreme experimental rigor does not forbid, but on the contrary permits and encourages the enthusiasm for the boldest speculations. (Monod 1967, 6)

Conclusion

In concluding this investigation on Monod's early work, I would like to emphasize three points that indicate directions for further researches on the history of French molecular biology.

(1) My first point directly concerns Monod's 1947 model of enzymatic adaptation. Even though Monod was to progressively deconstruct all the hypotheses he proposed in this model, nevertheless its general appearance already reveals typical aspects of the way Monod wanted to produce biological knowledge. On the one hand, the ultimate goal of this precise model was to provide a strictly mechanistic explanation of living properties, even though these appeared to be finalistic, especially when the perfect adaptation between the nature of the medium and the nature of the enzymes produced by the cell was concerned. In one way or another, Monod believed, nature had to be objective (Monod 1971). On the other hand, in its molecular working, this model was already based on interactions between different sub-units, where the shape of molecules was considered as the relevant level of explanation. This interest in the shape of proteins and the way it can be modulated was the starting point of what Monod always considered as his main scientific contribution (more important than the operon model): the model of allosteric transitions.

(2) My second point concerns the way in which Monod conceptualized the multicellular organism. In 1947, he had no problem applying a theory developed by Lwoff for explaining the phylogeny of unicellular organisms to the case of the ontogeny of multicellular organisms. This is an indication suggesting that Monod conceived of multicellular organisms as populations of cells. This idea was already fundamental for Georges Teissier and should be re-examined for Monod in light of his later achievements. It is known, for example, that Monod remained convinced – at the end, against Jacob – that *E. coli* was the best model organism to study the fundamental mechanisms of embryogenesis in metazoans (Jacob 1997, 86).

(3) My third point relates to the wider political context. In September 1948, Monod became directly involved in the "Lysenko affair." Lysenkoism should be seen as an external event that strongly reinforced Monod in his metaphysical choices. In this paper, I have argued that Monod, since the very beginning, had in mind to produce a non-teleological biology, and that this inclination was in the main a reaction against the finalistic atmosphere of French biology in the 1930s. Lysenkoism strengthened this aspect of Monod's researches and, more generally, was something like the ultimate challenge for scientists who founded the French school of molecular biology.

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