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The Contributions – and Collapse – of Lamarckian Heredity in Pasteurian Molecular Biology: 1. Lysogeny, 1900–1960

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Abstract. This article shows how Lamarckism was essential in the birth of the French school of molecular biology. We argue that the concept of inheritance of acquired characters positively shaped debates surrounding bacteriophagy and lysogeny in the Pasteurian tradition during the interwar period. During this period the typical Lamarckian account of heredity treated it as the continuation of protoplasmic physiology in daughter cells. Félix d'Hérelle applied this conception to argue that there was only one species of bacteriophage and Jules Bordet applied it to develop an account of bacteriophagy as a transmissible form of autolysis and to analyze the new phenomenon of lysogeny. In a long-standing controversy with Bordet, Eugène Wollman deployed a more morphological understanding of the inheritance of acquired characters, yielding a particulate, but still Lamarckian, account of lysogeny. We then turn to André Lwoff who, with several colleagues, completed Wollman's research program from 1949 to 1953. We examine how he gradually set aside the Lamarckian background, finally removing inheritance of acquired characters from the resulting account of bacteriophagy and lysogeny. In the conclusion, we emphasize the complex dual role of Lamarckism as it moved from an assumed explanatory framework to a challenge that the nascent molecular biology had to overcome.

Keywords: Lamarckism, Inheritance of acquired characters, Lysogeny, Molecular biology, Bacteriophage, Pasteur Institute, Jules Bordet, Eugène Wollman, André Lwoff

Introduction

The present article, the first of two closely linked articles, is the continuation of a long-term project, begun by Richard Burian, Jean Gayon and Doris Zallen in the mid-1980s (Burian et al., 1988; Burian and Gayon, 1999, 2004; Gayon and Burian, 2000). The project has two key aims. The first is to uncover the deep and hidden roots of some important concepts that contributed to the birth of molecular biology. The second is to outline the history of thinking about heredity in France from the mid-nineteenth century forward. These two aims are nicely conjoined given that the striking contributions of French biologists to molecular biology around the middle of the twentieth century drew on very different traditions than most other contributions to molecular biology. We were puzzled by the sources of those contributions and found it necessary to explicate them in ways that captured the importance of the deep history behind them. We remain convinced of the importance of deep history for understanding present concepts and fascinated by the richness of the historical developments in France.

Our new studies focus on the Pasteur Institute and, in particular, on the deep tradition that embraced Lamarckian inheritance within that institute. By the beginning of the twentieth century, after approximately two decades of significant work by French neo-Lamarckians in several distinct disciplines, French biologists were largely committed to neo-Lamarckian doctrines regarding evolution and heredity. Indeed, there were significant programmatic efforts to provide mechanistic and protoplasmic underpinnings for a neo-Lamarckian framework (Loison, 2010). By the 1920s, however, these efforts were clearly unsuccessful and most neo-Lamarckian thought took on a strongly negative tone, contributing among other factors to the specific French resistance to Darwinian evolution and Mendelian genetics (Burian et al., 1988). At the Pasteur Institute, there was considerable evidence for the seemingly Lamarckian adaptation of bacterial cultures and other pathogenic microorganisms exposed to various challenges and to different environments. As microbiology had not yet been impacted by genetics at the time, there was little or no countervailing evidence in favor of a selectionist rather than a Lamarckian interpretation of the "accommodation" of microorganisms to environmental change (Loison, 2013). As a result, even though the Pasteurians were not, by and large, caught up in

evolutionary disputes or debates over neo-Lamarckism, they were openly sympathetic to and often presupposed neo-Lamarckian points of view (Loison, 2010).

We argue that neo-Lamarckism had a significant influence on the handling of questions about heredity in the Pasteurian tradition. In spite of the generally negative character of neo-Lamarckian arguments at the time, neo-Lamarckism made important constructive contributions, some direct, others indirect, towards the establishment of French molecular biology. We acknowledge that, during the late 1940s and 1950s, most Pasteurian molecular biologists came to deny the inheritance of acquired characters and adopted a strongly anti-Lamarckian stance, but we argue that the Lamarckian tradition nevertheless played a major part in shaping the research programs on lysogeny and enzymatic adaptation during the interwar period.

The present article examines the overall Lamarckian stance of Pasteurian research on phage[1] and lysogeny from about 1920 to 1940 and the resolution of the problem of lysogeny achieved by André Lwoff and his co-workers after WWII. The second article will focus on the work of Jacques Monod and his colleagues on enzymatic adaptation. Both articles highlight the fact that Lamarckian heredity was originally a key ingredient of the description of the phenomena being investigated, but became the ultimate challenge for those researchers who, like André Lwoff, Jacques Monod, François Jacob and others, contributed to the decisive breakthrough on the problem of the regulation of gene expression after WWII. Since the concepts employed were long-lived and the problems were dealt with over several decades, there is some temporal overlap between sections of the two articles and between articles themselves. This approach allows us to show how concepts and problems were reframed, thus gaining a steady and progressive sense of the ways in which different lines of work interacted with each other and affected the conceptual landscape.

Given the complexity of the debates that we seek to understand, it is important to distinguish clearly between two phenomena that were at the heart of those debates, namely bacteriophagy and lysogeny. The phenomenon of bacteriophagy consists in the lysis of all or nearly all the cells in a bacterial population – i.e., their destruction by dissolving of

[1] We will use the common English shortening of this term to "phage" even though the French term has remained "bacteriophage" and "phage" did not come into general use in English until the late 1950s. When we translate texts and when it preserves the "feel" of what was said before the shift in terms solidified in English, we will retain "bacteriophage". But we intend no significant distinction between the terms "bacteriophage" and "phage".

their cell membranes. We now know that this lysis is the consequence of the reproduction of bacterial viruses (in the contemporary meaning of that term), i.e., bacteriophages that have infected the bacteria. But when the phenomenon of bacteriophagy was discovered, in the second half of the 1910s, several alternative explanations were concurrently put forward as we will see in section "Lamarckian Controversies About Bacteriophagy and Lysogeny at the Pasteur Institute: From Physiological to Particulate Heredity (1917–1943)", and the existence of clearly describable active bacteriophage was not immediately accepted as the obvious – or as the correct – explanation of the phenomenon.

Lysogeny is a distinct phenomenon, although it was often confused with bacteriophagy. In lysogeny, certain strains of bacteria maintain the ability, across a large number of generations, to cause other bacteria to lyse, even though they are, themselves, free of virulent bacteriophage particles. In other words, lysogeny is the hereditary power to cause lysis in other bacteria (and perhaps also the lysis of the lysogenic bacteria as well as those from other strains). Jules Bordet provided the name for this bacterial property, to wit '*pouvoir lysogène*' [lysogenic power] (Bordet, 1925). This phenomenon was described nearly simultaneously by Jules Bordet and Oskar Bail (Bordet, 1925; Bail, 1925). Like bacteriophagy, it was the subject of contradictory interpretations. For a long time, most students of bacteriophagy and lysogeny did not accept the controversial claim that certain bacterial strains are lysogenic and free of active bacteriophage, partly because it proved to be technically difficult to be sure that both the medium in which purportedly lysogenic bacterial cultures were raised and the bacteria themselves were entirely free of virulent bacteriophage particles. As we will see, the debates surrounding the existence and the physiological nature of lysogeny were of primary importance among French Pasteurians during the interwar period.

Regarding the issue of bacteriophagy, Ton van Helvoort has already put forward a very convincing case in favor of a conceptual distinction between endogenous and exogenous understandings of bacteriophagy during the period 1917–1957 (van Helvoort, 1992, and especially 1994b). Although this distinction remains relevant, we believe that, at least with respect to the more limited phenomenon of lysogeny as considered within the specific French context, another distinction is more illuminating. Around 1900, French neo-Lamarckians advanced a clear distinction between a physiological and a corpuscular conception of heredity. It is this distinction that directly shaped the theoretical framework within which the nature of lysogeny was later questioned and finally solved.

The first section of the paper describes the two opposing views of inheritance that were advanced in French biology at the end of the 19th and the beginning of the twentieth century. Because French neo-Lamarckism was a largely Bernardian theory, we claim that a physiological account of heredity was clearly favored, whereas particulate conceptions were strongly opposed and limited to the specific case of ''heredo-contagion''. As will soon be clear, this is why Mendelian genes were often dismissed as microbes at that time. Nevertheless, this Pasteurian-corpuscular view of hereditary factors later became a powerful tool in the hands of Eugène Wollman in the 1920s and 1930s.

The second section marshals evidence supporting our dichotomous reading of the debates surrounding first the nature of the bacteriophage and then that of lysogeny. We show that, as a typical Pasteurian, Félix d'Hérelle thought of the bacteriophage as an autonomous and pleomorphic microbe able to transform itself physiologically and evolve through the inheritance of acquired characters. We next turn to work conducted by Jules Bordet and his associates during the 1920s, which casts light on the puzzling phenomenon of lysogeny. We agree with van Helvoort that Bordet's explanation of lysogeny is an instance of the ''physiological style'' (van Helvoort, 1992). However, our specific claim is that the word ''physiological'' must not be understood in opposition to ''exogenous'' nor ''bacteriological'', but rather, more precisely, in opposition to ''corpuscular'' or ''particulate''. Whether the hereditary factor originates inside or outside the bacterial cell, Bordet explicitly stated that biological heredity is not reducible to morphological entities, but should be explained at the level of the entire protoplasm, which functions metabolically as a whole. Consequently, his conception of lysogeny as ''hereditary nutritive vitiation'' fits perfectly with the typical French neo-Lamarckian framework. This explains why Bordet was so firmly opposed to Eugène Wollman's interpretation according to which lysogeny could be understood in the terms of Darwinian pangenesis.

In the third and last section, we focus on the pivotal role played by André Lwoff and his colleagues around 1950 in the resolution of the problem of lysogeny. We show that Lwoff not only took up Wollman's research program but also transformed it in the light of his concept of an ''entity endowed with genetic continuity''. This concept, replete with potential Lamarckian implications, was essential in the formation of the hypothesis of the ''prophage''. It would therefore appear that the modern concept of virus was progressively constructed along two intricate theoretical lines: by a difficult stepwise separation from the concept of entity endowed with genetic continuity and, second, by

"molecularization" in terms derived from the findings and concepts of nascent molecular biology. In addition to André Lwoff, his protégés François Jacob and Élie Wollman were fundamental figures in this process of "de-Lamarckianization;" all three were very careful never to use the phrase "inheritance of acquired characters" in their work on lysogeny.

The Theoretical Core of Classical French Neo-Lamarckism: Heredity as the Continuation of Protoplasmic Physiology

Ernst Mayr has suggested that there was a fundamental conflict around 1900 between two "Weltanschaungen" regarding the nature of biological heredity. The "corpuscularists-preformationists-cytologists" were on one side, and the "physicalists-epigenesists-embryologists" on the other (Mayr, 1982, p. 772). The former thought of heredity in terms of discrete representative particles, whereas the latter envisaged it as the consequence of global functioning of cells or organisms. In putting forward this account, Mayr draws on a well-established distinction that biologists utilized at the beginning of the twentieth century, among the more important of them Thomas Hunt Morgan. For example, in 1910, before his conversion to Mendelism, Morgan described the opposition between these two ways of conceiving biological heredity as follows:

> The modern literature of development and heredity is permeated through and through by two contending or contrasting views as to how the germ produces the characters of the individual. One school looks upon the egg and sperm as containing *samples* or *particles* of all the characters of the species, race, line, or even of the individual. This view I shall speak of as the *particulate theory of development*. The other school interprets the egg or sperm as a kind of material capable of progressing in definite ways as it passes through a series of stages that we call its development. I shall call this view the *theory of physico-chemical reaction*, or briefly the reaction theory. (Morgan, 1910, pp. 449–450, emphasis in the original)

We take this distinction to be fundamental; it is found consistently in the specific context of French biology from 1880–1920. During this period French neo-Lamarckian thought was based on a protoplasmic theory of life and was strongly opposed to particulate conceptions of heredity. This protoplasmic theory was never precisely articulated or

embodied; nevertheless, it constituted a central aspect of French biology around 1900. In accordance with Claude Bernard, but also Ernst Haeckel and T. H. Huxley, most of the French neo-Lamarckians analyzed the main questions of General Biology in terms of the properties of living matter, i.e., protoplasm (Gayon, 1991, 2013; Loison, 2010, 2012). They presumed that by studying protoplasm and its dynamics they would ultimately solve the fundamental questions regarding the mechanisms of evolution, development, and heredity.

In 1895, Yves Delage, Professor of Zoology at the Sorbonne, published a book that became a milestone of French biology, *La structure du protoplasma et les théories de l'hérédité* (Delage, 1895).[2] In this imposing opus (878 pages in the first edition), Delage reviewed all the theories of the structure and activities of protoplasm, dividing them into two main categories (Delage, 1895, pp. 406–407). Theories of the first category treat protoplasm as an aggregate of molecules, understood in terms of the classical chemistry of the epoch. The morphological properties of cells and organisms were supposed to result from the physical and chemical interactions of these compounds with each other and with the external environment. From this point of view, protoplasmic physiology, interpreted as a dynamic process of the ensemble of molecules, was supposed to determine the course of embryological development and the traits of the adult organism. Theories of the second category treat protoplasm as an intermediate level of organization consisting of corpuscles with a definite morphology. These particles were endowed with the attributes required for life – nutrition, growth, and reproduction. Each of these particles was supposed to represent one or another of the characters of the future organism and entailed an overall conception of heredity. Delage claimed that Darwin's concept of gemmules, de Vries's concept of pangenes, and Weismann's concept of determinants all favored this latter theory.

Delage's distinction helps us to clarify the peculiarities of the French tradition from 1880–1920, a period during which most French biologists held a physiological conception of heredity and opposed particulate conceptions of heredity. One of the major intentions of French neo-Lamarckism was to extend and complete Claude Bernard's ultimate project of unifying morphological and physiological sciences (Loison, 2010, 2011). From this perspective, it was of fundamental importance to prove that protoplasmic processes served as the basis for both chemical

[2] This book quickly became a key reference work. A heavily revised version was published in 1903 with the simpler title, *L'hérédité et les grands problèmes de la biologie générale*.

and morphological syntheses. Protoplasm was thus conceived as a unitary material with totally integrated functions that could not possibly be separated into parts that were more-or-less independent, either in structure or in function.

It followed that reproduction was seen as a simple process that took place at the levels of the cell and the organism, and consisted in nothing more than the division of a mass of protoplasm in which each of the new parts preserved the nutritional dynamics of the initial protoplasm. Thus, in this period, French biologists explained the entire mechanism of heredity in terms of the continuation of the physiological state of the protoplasm. Such a conception of heredity is quite similar to the one held by T.H. Morgan from before 1900 to the middle of 1910, as indicated above. In its turn, it is easily distinguished from other non-particulate and dynamic conceptions of heredity like that developed, for example, by William Bateson. In effect, Bateson saw heredity as being, initially, a physical force propagating itself (Coleman, 1970) where the French neo-Lamarckians restricted it to a strictly metabolic and nutritive conception.

The principal empirical arguments for this physiological conception of heredity were based on experiments demonstrating the persistence of induced modifications in asexual reproduction, i.e., by direct transfer of protoplasm. In 1901, following the rapid expansion of the new genetics, Julien Costantin, a professor at the Museum of Natural History in Paris, thought it necessary to write a book reviewing the empirical support for the inheritance of acquired characters (Costantin, 1901). In this work, Costantin employed many arguments already derived from Pasteurian microbiology — inheritance of resistance acquired from vaccines, heritable variation of virulence in bacteria, etc. (Costantin, 1901, p. 68 ff.). He based his arguments directly on the explicitly neo-Lamarckian interpretations of these experimental findings already provided by Émile Duclaux (Gayon, 1995). Similarly, Costantin described some experiments with fungi, conducted most notably by the Belgian botanist Léo Errera. It is important to note that Errera, the first teacher of Jules Bordet, a major protagonist in the history examined below, was convinced of the efficacy of the inheritance of acquired characters as a physiological property of the protoplasm (Errera, 1899). It is therefore not surprising that during the 1920s Bordet also developed and supported a Lamarckian and physiological account of the hereditary phenomenon of lysogeny.

On a more theoretical level, Robert Olby has shown that the development of colloidal chemistry provided major support for the various

dynamic theories in physiology and embryology at the beginning of the twentieth century (Olby, 1986, particularly p. 293). Likewise in France, the dynamic and protoplasmic conception of heredity received support from the vogue for colloidology roughly from 1900 to 1930 (Loison, 2010, pp. 68–70). In effect, the concept of a colloidal state of matter allowed scientists to adopt a materialist framework and work out in a consistent way how cellular protoplasm could function as an integrated whole and how it could transmit innumerable transformations in its organization across the long series of cellular divisions. Neo-Lamarckian texts regularly include positive references to the colloidal state of living matter. For example, Félix Le Dantec, one of the most important neo-Lamarckians of the time, affirmed that "all material, while living, is in a colloidal state" and that this proposition constituted nothing less than the "keystone of all biology" (Le Dantec, 1907, p. 20, emphasis in the original).

Le Dantec was one of the fiercest opponents of the corpuscular conception. He began his career at the Pasteur Institute, where he was a student of Élie Metchnikoff and Alfred Giard. While he was at the Pasteur, he examined the digestive processes of several species of protozoa (Le Dantec, 1891) A few years later, however, he abandoned microbiology for the speculative pursuit of the grand questions concerning evolution and heredity. From 1895 until his premature death in 1917, he erected a vast explanatory system based on the concept of functional assimilation (Le Dantec, 1895, 1896). In several books he sought to demonstrate that all the characteristics of living beings follow directly from the ability of protoplasm to increase its volume by assimilating chemical compounds from the environment (Le Dantec, 1896). Heredity, he argued, is best conceived as the maintenance of the dynamic of exchange between the protoplasm and the environment over the course of generations.

In 1904, Le Dantec published an article in the *Revue Scientifique* that severely criticized Mendelian genetics and, more generally, all corpuscular theories of heredity (Le Dantec, 1904). He took direct aim at Lucien Cuénot, the only biologist in France with a program of research in genetics at the time (Burian et al., 1988). For Le Dantec, genes could only explain superficial or ornamental characters, and certainly not the hereditary processes responsible for embryonic development. He claimed that they should be understood as microbes that block the normal regulation of physiological processes and thus bring abnormal traits into existence. Mendelian heredity reveals the simple fact of *contagion*, a term that will be of central interest below (see especially

sections "Jules Bordet: Lysogeny as "Hereditary Nutritive Vitiation" and "Eugène Wollman: Rethinking Lysogeny from a Corpuscular Standpoint"):

> Mendelian heredity does not concern heredity, properly conceived, but rather a kind of *contagion* of which the gametes are the object. In any case, it is apparent that these phenomena of discontinuous heredity or of contagion will not teach us anything about the phenomena of continuous heredity, or heredity properly understood. *One cannot make a human by accumulating diatheses* [pathological dispositions], and the error of the theory of representative particles is, precisely, its belief that a human egg is formed by the accumulation of little microbes. The facts of Mendelian heredity may thus be said to be *accidents* superadded to normal heredity just as a disease is added to the normal physiology of an individual.[3] (Le Dantec, 1904, p. 515, emphasis in the original)

This article is important because it presents with perfect clarity the central disjunction between the physiological-protoplasmic conception of developmental heredity and a corpuscular conception of heredity in which the corpuscles are explicitly identified as microbes – autonomous living bodies within the economy of the protoplasm – capable of propagating their hereditary properties by infection.

From this historic moment onward, French biologists conceived the main relevant distinction as one between physiological and corpuscular conceptions of heredity and *not* as a distinction between Lamarckian and non-Lamarckian conceptions of heredity (i.e., between "soft" and "hard" heredity). We therefore employ the former distinction in our analysis of the debates regarding the explanation of bacteriophagy and lysogeny in the Pasteur Institute during the first half of the twentieth century. This distinction will also be used in the subsequent paper on enzymatic adaptation.

This physiological understanding of developmental variation, and heredity – as modes of modification of the nutritional regime of the protoplasm – was dominant in French biology until about the 1920s, prior to which the idea of particulate heredity was used exclusively for cases of hereditary transmission of contagious diseases by microbes. This position retained its authority within the Pasteur Institute, where neo-Lamarckian physiological conceptions also held sway well beyond the circles around Émile Duclaux and Félix Le Dantec. A particularly interesting case for the present study is that of the zoologist Félix

[3] Unless otherwise stated all translations are ours.

Mesnil. A pupil of Alfred Giard like Le Dantec, many of papers demonstrate his attachment to this form of Lamarckism (Loison, 2008). From 1907 until his death in 1938, Mesnil directed the Laboratory of Colonial Microbiology of the Pasteur Institute, which produced a succession of studies inspired by neo-Lamarckian views. Gabriel Gachelin and Annick Opinel have shown, for example, that the research in medical entomology conducted by Émile Roubaud in Mesnil's laboratory demonstrates a thoroughly Lamarckian orientation (Gachelin and Opinel, 2008). Roubaud appears to have conceived of heredity as a sort of progressive physiological reinforcement; it is noteworthy that he explained the formation of the races of parasitic insects as a function of the availability of potential hosts in this way (Gachelin and Opinel, 2008, p. 275). This was the very laboratory in which André Lwoff began his service in the Pasteur Institute in 1921, when he was barely 19 years old. Thus, Lwoff began his long and productive career in a situation strongly imbued with Lamarckian assumptions. We will come back to this point in the third section when we provide a brief overview of the work he conducted with Édouard Chatton in protozoology.

The early 1920s also saw the beginning of a long-term polemic within the Pasteur Institute regarding the nature of bacteriophage and especially of lysogeny. Over a twenty-year period the protagonists in this complex debate confronted each other with numerous conflicting hypotheses. In the next section we demonstrate that these hypotheses were framed precisely by the physiological versus the particulate conceptions of heredity. These alternative views are crucial for understanding the course of the complex debates that ensued.

Lamarckian Controversies About Bacteriophagy and Lysogeny at the Pasteur Institute: From Physiological to Particulate Heredity (1917–1943)

The early history of bacterial viruses has been well studied in several works, and we refer the readers to them in order to have a more detailed account of the story (Waterson and Wilkinson 1978; Varley 1986; Brock 1990, esp. chaps.6 and 7; Van Helvoort, 1994a). We will not present an exhaustive account of studies of bacteriophage in the interwar period here (Van Helvoort, 1992, 1994b), but rather focus on those aspects that reveal a particular relation between those studies and doctrines regarding heredity in the French setting. This theoretical aspect of the problem was especially important for the French biologists who first

worked on it. Accordingly, this section is limited to an examination of how the controversies at the Pasteur Institute fit into the conceptual distinction about heredity that we just promoted.

For about twenty years following the discovery of bacteriophagy[4] by Frederick Twort in 1915 (Twort 1915) and Félix d'Hérelle in 1917 (d'Hérelle, 1917), possible explanations of the lysis of bacterial colonies by filterable elements were conceived in two ways. In keeping with d'Hérelle, some believed that the lytic agent was a virus, i.e., in the theoretical context of the time, an ultramicroscopic microbe, invisible and able to pass through filters that could retain all known bacteria. This hypothesis implied that the lytic principle was a "microorganism" and therefore a living being, endowed with the fundamental properties of life, especially assimilation, physiological adaptation and reproduction. This hypothesis should not be confounded with what microbiologists today label a "virus" (see section "Beyond Lamarckism: Constructing the Molecular Definition of Virus").

On the other side were the defenders of the "diastatic" (i.e. enzymatic) interpretation, first proposed by Tamézo Kabéshima and Jules Bordet, who worked respectively at the Pasteur Institute of Paris and Brussels (Kabéshima, 1920a, b; Bordet and Ciuca, 1920a, b, 1921a, b). The enzymatic interpretation stated that the lysis of the bacterium was due to a non-living chemical agent (a "diastase"), produced by the bacterium itself, able to catalyze the formation of a similar pathogenic chemical in other bacterial cells. The common name for this hypothesis was "transmissible autolysis" (Bordet and Ciuca, 1920a). Although the defenders of this theory tried hard to impose this expression, rather than "bacteriophage", they never succeeded. As early as the mid-1920s, "bacteriophage" (or simply "phage") tended to become the name for the phenomenon itself, whatever its explanation.

Félix d'Hérelle: The Phage as a Pleomorphic Microbe

Félix d'Hérelle (1873–1949) began his turbulent career at the Pasteur Institute and he always remained related to it in some manner or other (for biographical and bibliographical details on d'Hérelle, see Varley, 1986 and Summers, 1999, 2014) From the very beginning, d'Hérelle was aware that two possible theories could account for the nature of the lytic principle he had discovered in the feces of dysenteric patients. It could either be a "filterable microbe" or be a "lytic diastase" secreted by

[4] We use the word "bacteriophagy" to designate the *phenomenon* described by Twort and d'Hérelle.

certain bacteria against themselves (or other bacteria) (d'Hérelle, 1918, 1919). But from the very beginning of his work on bacteriophage to the end of his career, d'Hérelle adopted an extremely dogmatic position on this issue: the lytic agent was a "living organism", an obligate parasite of bacteria, dependent on bacteria for its growth and survival. For this reason, it could be named "bacteriophage", that is to say an organism that "eats" bacteria. d'Hérelle quickly discovered that the aforementioned microorganism was active in a number of other bacteria such as the typhoid bacterium and *B. coli* (modern *E. coli*).

Consequently, the question arose whether or not there were distinct races or species of bacteriophage or whether there was only one species able to "adapt" itself to its various hosts and "acquire" through "habit" the capacity of developing in this or that bacterium (d'Hérelle, 1919, p. 1238). D'Hérelle was – and remained – no less dogmatic on this topic than on the subject of the nature of the lytic principle. There existed only one species of bacteriophage. But this unique species was able to adapt or "accustom itself" to various species of bacteria and to their changing characters and conditions of life. D'Hérelle said that "millions of strains" of bacteriophage (d'Hérelle, 1919) could be observed. But in all cases, they were obtained through the gradual habituation of a single species.

There can be no doubt about the kind of theory of heredity d'Hérelle had in mind for the explanation of the adaptation of bacteriophage. It was a typically Lamarckian physiological schema, requiring inheritance of acquired characters at the level of the whole microbe, as is evident from the following example in which the authors state how a strain of bacteriophage can adapt to different temperatures in the course of successive passages in a certain environment: "gradually, the thermoresistance becomes an acquired character transmitted to the descendants. […] There is thus no doubt that the acquired character of thermoresistance tends to become hereditary" (d'Hérelle and Sertic, 1930, p. 1257). And this process of physiological adaptation ought not be confounded with selection of preexisting resistant forms:

> If, during a gradual adaptation process, we raise the temperature abruptly at any time (e.g., from 58° to 62°), we observe that the formerly resistant particles are strongly attenuated and their descendants remain so. This phenomenon clearly shows that the bacteriophage undergoes a real adaptation and that it is not about selection of originally heat resistant particles. (d'Hérelle and Sertic, 1930, p. 1258)

In point of fact, the physiological and protoplasmic concept of heredity to which d'Hérelle adhered was also related to the concept of pleomorphism. Karl Nägeli first put this concept forward at the end of nineteenth century, at the very beginning of bacterial research. Nägeli claimed that there were no natural species of "microbes" or "virus" (synonyms in Nägeli's terminology), but only one single species, whose appearance varied as a function of the milieu. The classical Pasteurian interpretation of microbes was of course incompatible with this concept of pleomorphism. But Pasteur himself, as well as many of his pupils admitted that this theory was true for the so-called "races" of bacterial species. At this level, Pasteur, as well as Metchnikoff, Chamberland, and Roux, accepted a limited form of pleomorphism: bacteria of a given species could undergo important modifications of appearance and virulence in the course of passage through successive hosts. The changes in virulence ("attenuation" or "exaltation"), in particular, could be explained by the hypothesis that bacteria were able to transmit some acquired modifications to the following generations. Thus, in the field of microbiology, there existed a close relationship between the concept of pleomorphism and the Lamarckian physiological concept of heredity.

d'Hérelle never changed his mind (d'Hérelle, 1917, 1918, 1919, 1921, 1924, 1925, 1926; d'Hérelle and Sertic, 1930). For him, there was only one species of bacteriophage able to adapt itself in millions of ways, a doctrine that, in his mind, excluded the existence of true "races", specifically equipped for this or that bacterial host. This doctrine explains why d'Hérelle always refused to admit the existence of the many different viruses claimed to exist by various investigators: there was only one species of bacteriophage! D'Hérelle thus provides the first example of a strong interaction between the story of phage and Lamarckian inheritance. The case of Bordet will shortly provide a parallel problem for the concept of bacteriophage, but not at the same spatial scale. Bordet applied a Lamarckian and physiological understanding of heredity at the level of the whole bacterium in order to explain an unexpected phenomenon he called "lysogeny".

Jules Bordet: Lysogeny as "Hereditary Nutritive Vitiation"

Jules Bordet (1870–1961) wrote his first papers on d'Hérelle's phenomenon in 1920, just a year after he had obtained the Nobel Prize in Physiology or Medicine for his work on humoral immunity. Although he was Belgian, Bordet's scientific achievements cannot be separated from his involvement in the Pasteurian industry. In 1894, he went to Élie

Metchnikoff's laboratory at the Pasteur Institute. Later on, he became director of the "Institut Pasteur du Brabant" in Brussels, a position that he held until 1940. He published most of his major papers in the *Annales de l'Institut Pasteur* and his intense polemics with d'Hérelle developed in the *Comptes Rendus de la Société de Biologie* (Bordet and Ciuca, 1920a, b, 1921a, b; for Bordet's retrospective account in English of his views about bacteriophagy and lysogeny see Bordet 1931). Thus, in spite of not having French citizenship, Bordet incontestably belonged to the French-speaking community, and most especially to the Pasteurian network.

Bordet made his principal discoveries on hemolytic serums and agglutination during the five years that he spent at the Parisian Pasteur Institute. This work involved a comparison between bacteriolysis of cholera vibrios (by an antibody associated with a substance later called "complement"), and hemolysis. Bordet demonstrated that the mode of action of the hemolytic serums was entirely analogous to that of the bacteriolytic ones. Another important aspect of Bordet's work dealt with agglutination. He showed that it is obtained through the action of a specific protein, thrombin, which has the property of catalyzing the formation of more thrombin molecules.

These two lines of research make it clear why Bordet moved so fast, and was so self-confident when he began his research on the d'Hérelle phenomenon. Bordet was familiar with bacterial lysis and with physiological processes like agglutination, in which inanimate substances were able to induce the production of considerable quantities of substances of their sort. The concept of *transmissible autolysis*, which Bordet immediately opposed to d'Hérelle's hypothesis of the "bacteriophage", expressed his conviction that the d'Hérelle phenomenon could be interpreted on the basis of ordinary physiological processes.

The personal polemics between Bordet and d'Hérelle lasted almost a decade (1920–1928), but they structured much of the research on lysogeny among Pasteurians for thirty years until Lwoff's 1949–1950 experiments definitively established both the existence and the nature of lysogeny (section "How to Break with Lamarckism? Particulate Heredity, Genetic Continuity and the "Molecularization" of Virus (1949–1957)"). In the historical analysis that follows, it is important not to project later meanings onto Bordet's experiments and theories concerning "lysogenic power" and "lysogenic strains" – two expressions that he introduced as early as 1920. In particular, Bordet did not have available the notion of lysogeny that Lwoff later imposed on the field,

according to which lysogenic strains are those which are able to indefinitely perpetuate the ability to provoke the lysis of sensitive strains through their own lysis.

Tamézo Kabéshima, working at the Pasteur Institute of Paris, found d'Hérelle's phenomenon in a number of different bacteria living in various organisms, but contested the hypothesis of the "microbe" early in 1920 (Kabéshima, 1920a, b). Observing that the lytic principle was able to resist high temperatures, solvents, and antiseptics which ordinarily killed microorganisms, he denied that a living organism was involved and proposed that the phenomenon was caused by a "ferment" (enzyme) produced as a consequence of the action of some catalyst in the (multicellular) host able to induce the production of a similar substance by other bacterial cells (Kabéshima, 1920a).

Bordet's involvement with "d'Hérelle's phenomenon" was a consequence of the polemics between d'Hérelle and Kabéshima. Bordet insisted that the name that d'Hérelle gave to the phenomenon that he had discovered – " bacteriophage" – was improper because it was committed to an unproven, indeed, probably false, hypothesis, to wit, that a filterable microbe was responsible for the phenomenon. In the fall of 1920, he confirmed Kabéshima's denial of the living nature of the phage. He elaborated a significant account of his theoretical views in two papers written in collaboration with another Pasteurian, Mihai Ciuca. The first paper does not begin with a direct attack against d'Hérelle (whom Bordet always praised for his discovery), but with a solemn declaration about "heredity". Here is the first sentence: "The most surprising manifestations of life are reproduction, which allows the formation of a new being, and heredity, thanks to which this being looks like its parents" (Bordet and Ciuca, 1920a, p. 1293). This declaration is then followed by a full page of abstract phrases about heredity as the power of an individual organism to perpetuate a "variation" into the next generation that is itself manifested in reaction to a temporary and renewable external influence. This is obviously a classical Lamarckian schema, which, however, Bordet applies to an imaginary case involving contagion from one microbial cell to another in a certain culture, the contagion being due to the diffusion of a definite substance released by the cells in the medium. In such a case, the same variation will be both "hereditary" and "contagious":

> Suppose now that the cell being considered is a Microbe, and that the factor causing the variation is an active substance that the microbe elaborated at some point when acted on by a temporary external cause. We deduce from what precedes that the Microbe […] will pass on to its descendants the ability to produce the same

> substance […]. Let us imagine besides that the substance in question is diffusible in the culture medium. Then the variation can be not only hereditary but also contagious: the simple contact of the modified Microbe with the culture liquid in which it lived will suffice to imprint this modification on normal Microbes of the same species, which, in turn, will bequeath it to their posterity, which can themselves transmit it to normal microbes, and so on infinitely. (Bordet and Ciuca, 1920a, pp. 1293–1294)

Bordet and Ciuca then go on to treat d'Hérelle's phenomenon as an example of this theoretical schema. They claim that what d'Hérelle considered as a phenomenon of propagation of a parasitic microorganism (the bacteriophage) is actually ''transmissible autolysis''. Any new microbe that ingests the autolytic ferment is thereby enabled to produce this ferment through an autocatalytic process.

In their second paper, Bordet and Ciuca (1920b; see also 1921a) introduced the expression ''lysogenic power'' [*pouvoir lysogène*]. The idea was that a *culture* containing resistant bacteria can *acquire* a ''lysogenic quality''. Resistant bacteria were able to produce the ''lytic ferment'' (destroying other bacteria), while themselves remaining immune to it: ''The slimy-looking microbes, … [surviving from a largely lysed culture] represent *coli* that have resisted lysis and, even though they can develop abundantly in agar, are, henceforth and forever, carriers of the lysogenic quality'' (Bordet and Ciuca, 1920b, p. 1297). Thus, this ''lysogenic power'' can, itself, be transmitted indefinitely.[5]

In spite of their ambiguities, these papers introduced an exceptionally puzzling phenomenon, lysogeny, which remained under intense investigation for thirty years before there was a general consensus about the basic mechanisms involved. What happened to the term ''lysogeny'' is similar to what happened to d'Hérelle's term ''bacteriophage''. Just as ''bacteriophage'' rapidly became the name of a phenomenon in spite implying a certain hypothesis for this phenomenon, ''lysogenic strains''

[5] Although Bordet introduced the term ''lysogenic power'' in 1920, in 1925 he introduced the term 'lysogeny' in a lengthy review of his own work on lysogenic bacteria and his disagreements with d'Hérelle about the nature of bacteriophagy. In it, Bordet elaborated the concept of lysogeny in detail and provided evidence supporting its pertinence (Bordet, 1925). He argued that bacteriophagy could be caused by lysogenic bacteria in cultures that contained no viral particles and no 'living matter' from viruses. That paper is conventionally considered to be the major paper in which Bordet introduced the concepts of lysogeny and lysogenic bacteria into the literature. Another author, Oskar Bail (in Germany), introduced much the same concepts independently of Bordet at nearly the same time: both authors are credited for proposing the concepts of lysogeny as it pertains to lysogenic bacteria (Bail, 1925).

became the name of a phenomenon to be investigated, in spite of implying a certain hypothesis put forward by Bordet. Shortly after publishing the two 1920 papers already discussed, Bordet added his lifelong commitment that lysogenic strains not only perpetuate and release the lytic principle, they did so *without being lysed themselves*, that is to say, they only *secreted* the lytic principle, whereas other strains reacted to it by producing the same lytic principle and liberating it through their own lysis. It was André Lwoff who finally established in 1950 that lysogenic bacteria liberate phage only by lysing themselves (section "How to Break with Lamarckism? Particulate Heredity, Genetic Continuity and the "Molecularization" of Virus (1949–1957)"). Regardless, we now have a relatively clear picture of what Bordet (with the help of Ciuca) claimed to have introduced. Firstly, he proposed a different interpretation of d'Hérelle's phenomenon (transmissible autolysis); secondly, he claimed to have discovered a phenomenon unknown to d'Hérelle, namely, lysogenic strains. In both cases, heredity was a major theoretical concern. Transmissible autolysis was a case of "heredo-contagion", since the cells transmit a pathological power horizontally through a diffusible inanimate substance. Lysogeny was also a case of "heredo-contagion" in a second sense: certain bacterial cells perpetuate the power of producing the lytic principle vertically (i.e., through generations) without being killed themselves.

Eugène Wollman: Rethinking Lysogeny from a Corpuscular Standpoint

Bordet's Lamarckian penchant did not escape Eugène Wollman (1883–1943), who would later play a prominent role in the history of lysogeny. In 1920 he published a brief paper that sought to establish a parallel between Bordet's and Ciuca's "transmissible autolysis" and Darwin's pangenesis:

> It seemed interesting to us to take up the analogy between these ideas [of Bordet and Ciuca] and those put forward by Darwin in his hypothesis of pangenesis, which, in the mind of the illustrious English biologist, ought to supply a *provisional* schema for the mechanism of heredity in general, and the transmission of acquired variations in particular. […] Applying the images supplied by the pangenesis hypothesis to the interpretation of the d'Hérelle phenomenon is sufficient to yield the representation proposed by Bordet and Ciuca of the mechanism of this "hereditary nutritive vitiation". Darwin's gemmules become Bordet and Ciuca's "in-

> tracellular factors''. (Wollman, 1920, pp. 1478–1479, emphasis in the original)

Bordet and Ciuca employed the term ''intracellular factor'' (in the singular, not the plural) in their first joint paper (Bordet and Ciuca, 1920a, p. 1293). Wollman proposed a very personal interpretation of it in terms of particulate heredity that did not figure in Bordet's account. Wollman's invocation of pangenesis is the starting point of his interpretation of bacteriophage as consisting of material ''hereditary factors'', an interpretation that Bordet would not have accepted, and which, indeed, he refused.

Here we cannot examine the rich and vigorous debate that developed between Bordet and a number of Pasteurians in the 1920s in the detail that it deserves. The phenomena proved to be much more complex than anyone expected. But Bordet systematically emphasized that lysogeny posed fundamental problems regarding the meaning of ''heredity'' for bacteria. In one of his last big papers on this subject (Bordet and Renaux, 1928), he criticized Wollman's way of handling the problem of the relation between heredity and the lytic principle. By 1928, Wollman had clearly proposed that Bordet's lytic principle should be considered as the ''material bearer of a hereditary character'', similar to the chromosomal elements studied in Mendelian genetics (Wollman, 1925). Bordet refused to see the lytic principle as a ''materialized hereditary property''. For him, heredity was to be interpreted as a physiological phenomenon rather than in terms of definite material particles. The concept of heredity that he advocated was indeed the physiological-protoplasmic concept at the root of French neo-Lamarckism:

> If one abstracts from the phenomenon of sex […], heredity is only a regulation […] that persists for innumerable cellular divisions […]. When microbes are at stake, what we improperly call heredity is only the *continuation*, the indefinite unfolding, through the repeated divisions, of a purely *individual physiology* […]. In the absence of sexuality, for example in microbes, there is no proof that the faculty of perpetuating characters of the species is strictly localized: a great many substances, such the lytic principles, (or else all the living matter in all its complexity) may collaborate in the transmission of specific qualities *without allowing us to say that one of these agents represents, strictly speaking, the exclusive material bearer of such and such a property*. (Bordet and Renaux, 1928, pp. 1306–1307, emphasis added)

It is hard to decide whether these sentences are Bernardian or Lamarckian. For example, Bordet's treatment of heredity is very similar to some of Claude Bernard's declarations about heredity, such as "heredity is no more than the continuation or the memory of previous states experienced by the organisms" (Bernard, 1872, p. 309; for more, see Gayon, 1991, 2013). In contrast, Wollman's conception was more morphological. From the very beginning, Wollman had insisted on combining genetics with Lamarckism in order to provide a suitable explanation of lysogeny (Wollman, 1925, 1927). His repeated identification of the lytic ferment as a "genetic factor" or later as a "Mendelian gene" leaves no doubt about the fact that, in this particular case, he thought of heredity in terms of the continuity of a morphological structure, not as the continuation of a physiology (Wollman, 1928). The long-lasting opposition between Bordet and Wollman (1920–1928) must then be seen as an opposition that took place *within* the boundaries of Lamarckism. Bordet's approach belongs firmly within the physiological tradition of French neo-Lamarckism. In contrast, Wollman restored some credibility to including morphological considerations, and specifically particulate entities and their features, among the causes of the phenomena of "heredo-contagion".

Nonetheless, for this reason, Wollman should not be seen as breaking totally with the French neo-Lamarckian tradition. From the nineteenth century, that tradition explicitly held that instances of pathological heredity (but not developmental heredity) could be explained satisfactorily by hypotheses involving microbial particles capable of being perpetuated across long chains of generations. Indeed, recourse to the Darwinian hypothesis of pangenesis to explain pathological phenomena was not exceptional in the circle of Pasteurian biologists in Wollman's day. For example, Louis Blaringhem (a neo-Lamarckian who, among other things, was a "chef de service" at the Pasteur Institute 1909–1912) employed terminology very similar to that of Eugène Wollman when he interpreted certain results regarding the silkworm disease pebrine. Thus, in 1923 (without making any reference to Wollman) he wrote:

> In 1868, the year in which Pasteur provided definitive experimental proof establishing that the parasite that causes pebrine is inherited, Darwin put forward, timidly, the *hypothesis of pangenesis*, subsequently much debated. Hugo De Vries replaced pangenesis with intracellular pangenesis, the source of his studies of the mutability [by large discreet mutations] of species (1889). […]

> I have no intention of arguing for the validity of all of Darwin's arguments in favor of his hypothesis, the majority of which are wrong, but I suspect that all too often, in *explaining numerous aberrant phenomena of heredity*, the incidental circumstances in which particles that persist through sexual reproduction can be introduced into a given organism are neglected. If such particles are living, [they can] divide and affect all the ovules ([as do] molds that infect seeds of rye grass). (Blaringhem, 1923, pp. 166–168, emphasis added)

Lysogeny was typical of the "aberrant phenomena of heredity" and, as such, belonged squarely within the French neo-Lamarckian tradition. It was therefore legitimate to apply particulate and morphological explanations to it. What distinguishes Wollman from others is, on the one hand, his regular recourse to the concept of *Mendelian factors* and, on the other, that he thought that this type of particulate explanation could be generalized and extended beyond the domain of pathological heredity. A significant consideration here is that before beginning his career in the Pasteur Institute, Wollman had spent three years (1906–1909) as an assistant of Edouard van Beneden in Liège. Thanks to this, he may have been more inclined than most French neo-Lamarckians to treat morphological heredity positively, i.e. to take into account the possibility that discrete structures such as chromosomes could cause certain cellular properties.

From 1920 to 1943, Eugène Wollman, in close collaboration with his wife Elisabeth, spent much of his time studying lysogeny experimentally in several species of bacteria (Wollman and Wollman, 1925, 1932, 1936, 1938). As time went on, he reinforced the genetic component of his hypothesis, but always linked it to the general idea of the inheritance of acquired characters (see for example Wollman, 1927, pp. 914–918). We remark here that Wollman used the term "inheritance of acquired characters" frequently in connection with the transmission of the lysogenic power, whereas, in the early 1950s, André Lwoff and François Jacob took great pains not to use it (section "Beyond Lamarckism: Constructing the Molecular Definition of Virus").

Wollman's interest in genetics was based on the acknowledged physical stability of the gene. For Wollman, the stability of Mendelian factors was pivotal and necessary in order to explain "contagion", i.e. the horizontal transmission of the lysogenic power: the gene-bacteriophage had to be stable enough that it could be transmitted to bacteria through the external medium without alteration (Wollman and Wollman, 1932, pp. 73–74). Moreover, the intrinsic stability of the gene

could also be key for explaining how a modified metazoan gene (an acquired character) could be transmitted through the extracellular environment and then reach the germ line, thereby becoming truly hereditary (Wollman, 1927, p. 914). Wollman was clearly thinking of the bacteriophage as a model system for a general mechanism for the inheritance of acquired characters.

By the 1927 and 1936 *Mémoires* (Wollman, 1927; Wollman and Wollman, 1936) the Wollmans had begun to articulate a clear position, one that they did not consider to be well-supported experimentally until 1937 (Wollman and Wollman, 1936).[6] According to this position there are two phases in the life history of phage. In one phase, phage are found as particles, either free outside bacterial cells or, for a brief time, inside bacterial cells. The second phase (with no detectable phage particles) occurs most clearly in lysogenic cells. Experimentally, the Wollmans developed strong (but not absolutely decisive) evidence that when lysogenic cells of *Bacillus megatherium* in cultures with an extremely small number of free phage particles[7] are lysed by lysozyme no new phage particles can be found (Wollman and Wollman, 1936). From this they concluded that bacteriophage in lysogenic cells exist as some sort of *Anlage*, which they thought of as a stable Mendelian gene. This account explains how lysogenic bacteria retain the capacity to produce phage particles; they contain some sort of stable genetic material required for producing phage particles. The important point is that lysogenic bacteria do not contain phage particles at all (Wollman and Wollman, 1936, 1938).[8]

Eugène Wollman was keenly aware of how far he was from having demonstrated that his theory was sound. After the Nazis occupied

[6] Their position was clear enough in the 1936 *Mémoire* that Burnett and Lush, writing about bacteria that we would now characterize as phage-sensitive bacteria that had been altered to being phage-resistant and lysogenic by exposure to the relevant bacteriophage, claimed that "it is not [yet] possible to say whether this … change results from an altered genetic constitution of the bacterium or is directly induced by the associated phage at each generation. According to Wollmann's [sic] [1936] hypothesis the distinction between the two alternatives would disappear, the phage being regarded as a gene re-introduced into the genetic make-up of the organism."

[7] It was impossible at this time to obtain cultures of lysogenic cells with absolutely no free phage particles.

[8] By the end of the 1930, the distinction between Wollman's and Burnet's views turned on the fact that Burnet held that lysogenic bacteria contain living phage in a latent, incompletely developed form (a 'virus') (Burnet, 1936, pp. 346 ff.) while Wollman held that lysogenic bacteria contain an Anlage, a Mendelian gene, so that when the bacterium produces a phage, the phage develops from something that is not itself a phage (Wollman and Wollman, 1938; see also Lwoff, 1953b, pp. 277–278).

Paris, he and Elisabeth faced very difficult circumstances. He was barred from publishing and forced to leave his laboratory. He took refuge in Lwoff's laboratory, where, Lwoff reports, Wollman recognized the necessity of following events in single bacterial cells rather than performing a classical statistical analysis of the behavior of populations of bacteria. He planned to work with *Bacillus megatherium*, which he knew to be suitable for the purpose and to obtain a Fonbrune micromanipulator and other suitable laboratory equipment to pursue the quest to gain control of the production of phage particles by lysogenic bacteria and develop a definitive account of lysogeny and lysogenesis (Lwoff, 1988, pp. 74–75). The Wollmans were still trying to begin this project in December 1943 when the French police arrested them at the Pasteur Institute at the behest of the Nazis.[9] The archives of the institute own an unpublished and unfinished typescript Eugène Wollman wrote during the last years of his life entitled *The bacteriophage and the problem of ultraviruses* [*Le bacteriophage et le problème des ultravirus*]. At p. 284, in the last sentence of the text, he regrets that the "determination [of lysogeny] still escapes us completely" (Wollman, 1939–1942, p. 284). Completion of his corpuscular and genetic conception of the bacteriophage had to await the development of the experimental research program on lysogeny on which the Wollmans had hoped to embark. The success of Lwoff and later Jacob when they took up Wollman's research program rested mostly on the fact that Lwoff, in 1950, finally managed to discover culture conditions that could induce lysis in lysogenic strains of bacteria (section "How to Break with Lamarckism? Particulate Heredity, Genetic Continuity and the "Molecularization" of Virus (1949–1957)").

It is indisputable that Lwoff's general account of the nature of the bacteriophage was very close to, and rooted in, the corpuscular understanding of heredity that Eugène Wollman put forward in opposition to the classical neo-Lamarckian physiological account. Lwoff himself had already perceived this essential dichotomy. For instance, in 1965, in his Nobel lecture, he insisted on the fact that the physiological view of Bordet was an obstacle to conceiving the bacteriophage as a transmissible structure. He wrote:

> Nevertheless, it is of interest to note that the great immunologist did not conceive that heredity might be linked to a structure. For Bordet, *heredity was the perpetuation of an individual physiology*. The bacteriophage is not a materialized hereditary property, and

[9] Eugène and Elisabeth Wollman were sent to Auschwitz where they both died.

> Bordet affirmed in 1931: ''The invisible virus of d'Hérelle does not exist. The intense lytic activity represents a pathological exaggeration of a normal function of the bacterium'' [(Bordet, 1931)]. It seems strange to us today that such an eminent mind could have conceived of specific functions independent of any specific structure. (Lwoff, 1999, p. 177; emphasis added)

The controversy between Bordet and Wollman, as we have insisted, must be understood as the opposition of two ways of understanding the inheritance of acquired characters, physiological versus particulate. This episode shows that Lamarckism was still looked upon positively at the Pasteur Institute during the interwar years and that Lamarckian perspectives helped frame the debates surrounding heredity and contagion. In the next section, we show that the attitudes of the French Pasteurians who were involved in the work on bacteriophagy and lysogeny after WWII shifted with respect to the issue of Lamarckism. Lwoff and his associates faced the challenge of explaining an apparently Lamarckian phenomenon in strictly molecular and genetic terms.

How to Break with Lamarckism? Particulate Heredity, Genetic Continuity and the ''Molecularization'' of Virus (1949–1957)

The resolution of the problem of lysogeny took place after WWII in André Lwoff's laboratory, the ''Service de physiologie microbienne''. Lwoff was thoroughly familiar with the earlier disputes about bacteriophage and lysogeny in the Pasteur Institute and was a close friend of Eugène and Elisabeth Wollman. When Lwoff turned to the problem of lysogeny, he hoped to demonstrate the soundness of Eugène Wollman's stance on the topic (Lwoff, 1972, 1988). However, Lwoff never even mentioned the possibility that lysogeny could be interpreted as an example of inheritance of acquired characters, a leitmotiv that was central to Eugène Wollman.

To understand Lwoff's approach to the problem, it will be useful to begin with a brief sketch of the developments that occurred during the 1930s and 1940s, in the context of his collaboration with Édouard Chatton (1883–1947) concerning particles endowed with ''genetic continuity,'' a concept that played a continuing role in his work on lysogeny and the nature of bacteriophage (for a more detailed account, see Burian and Gayon, 1991, and Galperin, 1994).

The (Lamarckian?) Concept of an ''Entity Endowed with Genetic Continuity''

André Lwoff (1902–1994) began his career as a protozoologist under the aegis of Chatton in the summer of 1921. That fall, with Chatton's support, Lwoff was accepted into the laboratory of Félix Mesnil at the Pasteur Institute; however, he spent his summers, except during WWII, working collaboratively with Chatton in various marine biological stations until the latter's death in 1947 (Lwoff, 1971, 1988). By 1939 they had published fifty articles together, sometimes with others, on the development, evolution, life cycles, and morphology of a variety of protozoa, most of them ciliates.[10] By the 1930s Chatton and Lwoff were developing the concept of particles endowed with genetic continuity, a concept that Lwoff introduced into his subsequent work (Galperin, 1987). In Lwoff's vocabulary, that of a protozoologist interested in morphogenesis, ''genetic continuity'' applied to ''self-reproducing bodies endowed with specificity'' (Lwoff, 1950a, p. 15). Of central importance in this connection were their arguments for the genetic continuity of kinetosomes and of what they called the ''infraciliature'' of ciliates. Kinetosomes are the cytoplasmic particles responsible for the production of cilia. Ciliates, of course, have cilia, generally retained during their entire life cycle. But many parasitic ciliates, some of them pathogenic, are exceptional in this regard.

The patterns of organization of kinetosomes at different stages of a ciliate's life cycle are species-specific and can be surprisingly distinct. At each stage, a ciliate has a particular number of rows of kinetosomes (with or without cilia), organized in a characteristic way, with specific row lengths and numbers of kinetosomes in each row and geometries for the rows.

Starting in the late 1920s, Chatton, Lwoff, and colleagues produced a trove of new findings on ciliates. They reported that use of a silver stain, adapted from a version employed by Bruno Klein (Chatton and Lwoff, 1930), enabled them to show that the ''infraciliature'' at each stage in the life history of the ciliates in any given species was a constant cytoplasmic structure. One of Chatton and Lwoff's most controversial claims was that all kinetosomes derive from kinetosomes just as all cells derive from cells. Various others, e.g., Bruno Klein, argued that kinetosomes are produced *de novo* in a variety of situations. The heart of the

[10] Lwoff also developed a second line of work on the nutrition of protozoa during the same period, which yielded results of considerable general importance regarding growth factors and vitamins.

claimed genetic continuity of kinetosomes is that they are all generated from kinetosomes and that kinetosomes are autonomous in many of the ways that cells are. The point is not that kinetosomes are independent of the relevant environment(s), but rather that they are able to reproduce in the right circumstances by producing the necessary parts out of available materials (Chatton et al., 1929a, b, c, 1931a, b, c, d, e). One should emphasize here that the term ''genetic'' did not refer to the science of genetics, but was used in the original sense of the word, which refers to the ''genesis'' or ''development'' of something.

Genetic continuity, Lwoff argued later, is independent of hypotheses such as the plasmagene hypothesis and can be used to support investigations of other entities hypothesized to be endowed with genetic continuity (Lwoff, 1949, 1950a). It is striking that Lwoff's original support for the existence of particles with genetic continuity – and for the development of the concept of entities endowed with genetic continuity – was based on solid collection of microscopic evidence and not on theoretical considerations. As a microscopist and systematist, he was convinced that the best way to establish genetic continuity and to determine the powers that should be ascribed to bodies with genetic continuity is to work with observable bodies available to biochemists, morphologists, physiologists, and systematists, and he considered kinetosomes to be of general interest precisely for that reason (Lwoff, 1949).

One complication worth noting is that in some special cases, Chatton and Lwoff argued for a distinction between direct (or immediate) genetic continuity and indirect (or mediate) genetic continuity. A clear example in parasitic ciliates is provided by kinetoplasts,[11] which, in some organisms, are not (directly) descended from kinetoplasts. They are produced by kinetosomes that are descended directly from kinetosomes present at every stage in the life history of the ciliate and always produced by division of kinetosomes rather than *de novo*. Thus the (re)generation of kinetoplasts is recognized as a case of indirect genetic continuity. When Lwoff turned to bacteriophagy and lysogeny, he rethought some of the issues raised by indirect genetic continuity (see below section ''Beyond Lamarckism: Constructing the Molecular Definition of Virus'').

While it was built on a solid base of microscopic observation of visible particles, including chromosomes and chromomeres (Chatton

[11] Kinetoplasts are small granules produced together with cilia that were sometimes interpreted as an enlarged basis for the production of the cilium, sometimes as a separate body (Lwoff, 1950a, chap. 3).

et al., 1929c), the concept of genetic continuity was nevertheless not free of theoretical consequences. Firstly, this concept could also be applied to entities provided with theoretical descriptions that were not (yet?) visualizable or safely visualized. Examples include cytoplasmic plasmagenes and bacteriophage in lysogenic bacteria that had no visible phage. And secondly, in keeping with the general neo-Lamarckian tradition at the Pasteur Institute, it was physiologically based and was connected to the conception of "living matter" with continuity of structure and process. It thereby reflected some special characteristics of life, such as nutrition, (self)-reproduction and hence heredity. During the 1930s, Lwoff thought of entities endowed with genetic continuity as autonomous *living* particles (see especially Lwoff, 1932, p. 143). Moreover, if a particle endowed with genetic continuity could be acquired – or lost – by a cell in some way or another, it directly followed that the new character would necessarily become inherited. It is precisely an explanatory framework of this kind that was put forth by Eugène Wollman during the interwar years with respect to lysogeny.

It is important to keep in mind that the theoretical context of the work of Chatton and Lwoff on parasitic ciliates was filled with Lamarckism. As far as we know, there is no published article in which Lwoff, either alone or in association with Chatton, referred to the inheritance of acquired characters during the interwar period. On the other hand, Chatton was far more explicit and assumed a Lamarckian position on several occasions. For instance, in 1937, he did not hesitate to write that the morphological adaptations of ciliates remained inexplicable without considering "the inheritance of acquired characters" (Chatton, 1937, p. 40). In light of this it would be surprising, if Lwoff himself were not at least partly convinced of the adequacy of Lamarckian perspectives for providing a complete explanation of the evolution of parasitic ciliates.

If that likely hypothesis is true, it means that Lwoff progressively changed his mind during the 1940s as regards the validity of Lamarckism and its explanatory power. Our claim is that Lwoff's success, when he later turned to lysogeny, was first based on his ability to use genetic continuity as an interpretative matrix. But, at the same time, he also distanced himself greatly from the initial Lamarckian overtones that surrounded the concept of entity endowed with genetic continuity.

Nevertheless, although Lwoff remained vigilant to exclude Lamarckian phrases during the 1950s, it is striking to note that at least once late in his life, in 1990 at the age of 88, he wrote an article with obvious support for inheritance of an acquired character: the title of the article

published in the *Comptes rendus de l'Académie des sciences de Paris*, is explicit: "The organization of the cortex in ciliates: an example of inheritance of an acquired character." Lwoff's primary argument in support of this claim is that the cortex "plays a determining role in the arrangement of kineties [rows of kinetosomes] and that its organization is not commanded by the genome, but behaves as an acquired hereditary characteristic" (Lwoff, 1990, p. 109).

Lwoff's Resumption of Eugène Wollman's Research Program: An Overview

Before André Lwoff began personal research on bacteriophage, he already had a long-standing interest in the topic, reaching back to the very beginning of his career at the Pasteur Institute. He became acquainted with Eugène Wollman at about when the latter took up the problem of lysogeny. Wollman, who liked to discuss his ideas and the results of his experiments, sought to interest the then twenty-year old biologist in this new field of research (Lwoff, 1988, pp. 73–75). Lwoff remained aware of the progress of research on phage before 1949, as is shown by the fact that he discussed the question of the nature of phage in passing in his writings on five distinct occasions, including discussion of specific experimental findings (Lwoff, 1926, 1932 (his doctoral dissertation), pp. 140–144, 1936, 1944, pp. 185–191, 1947). In particular, thanks to his close connection to Eugène and Elisabeth Wollman, Lwoff was fully abreast of Eugène Wollman's conceptions and of the relationships that he had established between viruses and genes.

An international colloquium entitled "Biological Units Endowed with Genetic Continuity" took place in Paris in June 1948, one year after the death of Édouard Chatton. This symposium was organized with support from a Rockefeller Foundation grant to the Centre National de la Recherche Scientifique (CNRS) for international conferences aimed at reviving French science after WWII and connecting French scientists to international colleagues and to recent scientific developments elsewhere (Zallen, 1989). It is not entirely clear who organized the meeting, but Lwoff and Boris Ephrussi both had a major hand in it.[12] Papers derived from the meeting were published in French as *Unités biologiques douées de continuité génétique* (1949). Max Delbrück gave a talk on bacteriophage and Phyllis Rountree a talk on lysogeny, topics that were already important to the development of

[12] No editor is identified for the volume and no front material provides details about the organization of the meeting.

what would become molecular biology. Three other papers addressed a related topic, namely, plasmagenes. At the time, some scientists expected plasmagene hypotheses to yield solutions to problems in numerous domains, among them enzymatic adaptation, bacteriophagy, and lysogeny.

One indirect effect of the colloquium was that André Lwoff became definitively interested in working on lysogeny. Several months after the colloquium, Lwoff centered the work of his "Service" on this new domain of research, probing questions relative to the nature of phage by concentrating primarily on the lysogenic phase of the bacteriophage life cycle. In a not yet published autobiographical typescript written in 1988,[13] Lwoff lists three considerations that led him to focus on this topic in 1949: (1) the completion of his programs of research in protistology; (2) Monod's reflection on lysogeny in 1945 (Monod had written an unpublished manuscript on the subject that is lost today) and (3) the discussions in the colloquium of 1948, which had "sensitized" him to the importance of the topic.

As Charles Galperin has shown, at that time the majority of microbiologists denied the very existence of lysogeny. Importantly, this was the opinion of Delbrück, the preeminent sparkplug of the nascent "phage group" (Galperin, 1987). Even though Lwoff resisted the claim that Delbrück's denial of the reality of lysogeny was a key to his taking up the topic (Lwoff, 1988, p. 83), it was nevertheless part of the challenge that Lwoff took on when he chose to pursue (and vindicate?) Eugène Wollman's research program. In addition, Élie Wollman, Eugène and Elisabeth's son, had joined the Pasteur Institute after the war. Starting in 1946, he pursued research on bacteriophage and lysogeny in Lwoff's "Service" (Monod and Wollman, 1947). Thus when Lwoff took up this line of experimental work himself shortly before Élie Wollman left for Pasadena to study the genetics of bacteriophage with Delbrück, Lwoff's laboratory had already started working on the lysogeny.

Lwoff explicitly chose to take up Eugène Wollman's unfinished project concerning lysogeny when he began his own phage research with his colleagues. Lwoff recognized, with considerable appreciation, that he and his colleagues owed their success in solving the problem of lysogeny between 1949 and 1953 in good part to accepting Wollman's choices for advancing research on that topic (Lwoff, 1988, pp. 74–75). However, it would be inexact and excessively reductive to think that Lwoff was simply content to follow in Wollman's footsteps. The choice

[13] Publication is in progress (2016).

of working with a single bacterial cell reflects Lwoff's own scientific style and priorities at least as strongly as it mirrors Wollman's approach. Lwoff reported on several occasions (and this is a cardinal difference between him and Monod) that, as a morphologist, he was not at ease with statistical analysis and that he always preferred to work on the level of individuals rather than the level of populations (Lwoff, 1966, p. 89). His formation as a protozoologist and his experimental tastes shaped his systematic preference for working at the microscope, as François Jacob[14] and Georges Cohen[15] have confirmed to one of us. And, in fact, Lwoff began his research on lysogeny as a protozoologist, not as a bacteriologist.

The main challenge for Lwoff and his collaborators was to develop the means to provide a rapid and definitive resolution to the principal questions initiated by the debate that began twenty-five years earlier within the Pasteur Institute (see section "Lamarckian Controversies About Bacteriophagy and Lysogeny at the Pasteur Institute: From Physiological to Particulate Heredity (1917–1943)" above). As we show below (section "Beyond Lamarckism: Constructing the Molecular Definition of Virus"), Wollman's ideas were particularly helpful in constructing a fruitful theoretical scheme closely connected to the experiments undertaken by Lwoff and his colleagues. The concepts that Lwoff elaborated during this period contributed to the construction of molecular biology at the same time that they made a definitive break with the neo-Lamarckian background from which they came.

Using the tools available at the time for handling growing populations of bacteria and measuring the relative abundances of bacteria to phage, the problem whether phage are secreted by bacteria without lysing or whether phage are produced discontinuously (i.e., in a batch, with a large number of phage produced at once), could not be solved (Lwoff and Gutmann, 1950, p. 730). As Eugène Wollman had suggested, to resolve such questions it was necessary to change methodologies, to leave mass cultures aside and concentrate on the study of isolated bacteria. In 1949, Lwoff began acquiring the material necessary for carrying out such experiments. He bought a Fonbrune micromanipulator as well as a microforge for fashioning extremely fine micropipettes (Lwoff, 1988, p. 76). He ordered a custom-made plastic box equipped with a heater and thermostat large enough to hold a microscope and a micromanipulator. He also obtained a lysogenic strain of especially large *Bacillus megatherium* that provided the best-adapted material for the purpose in hand.

[14] Interview by LL, 25 October, 2010.

[15] Interview by LL, 8 November, 2011.

With Antoinette Gutmann, his new assistant, he began to work in the laboratory. The extreme complexity of the technique of micromanipulation that was required is particularly noteworthy. Lwoff's projects in this period could not have succeeded without the exceptional skill and dexterity of the experimenters and the care with which they worked at the laboratory bench (Lwoff, 1988, p. 76).

To summarize the problems tackled by Lwoff and his colleagues in 1949, it is useful to see how they subdivided their overarching question, namely, *is lysogeny a property of a strain of bacteria or of an individual bacterium*? To settle this issue, Lwoff and his collaborators took up a series of subsidiary questions: (1) Are bacteriophage liberated continuously or discontinuously? (2) How is lysogeny transmitted? (3) How are viruses liberated by bacteria, i.e., by secretion or by lysis of the bacteria? (4) What determines or triggers this liberation?

The first three questions received definitive answers in rapid succession during September and October 1949 (Lwoff and Gutmann, 1949a, 1949b, 1949c). Early experiments demonstrated unambiguously that the production of phage is extremely discontinuous and that production of phage by a lysogenic strain is independent of the growth of a culture of that strain. The phage-induced lysis of a bacterium, even a lysogenic bacterium, appeared to be irregular and unpredictable or, perhaps, to be a purely contingent event. Together with other evidence, these results showed decisively that the existence of a lysogenic population could not be explained by the steady secretion of viral particles in a growing culture. Elimination of the hypothesis that phage are secreted by bacteria in their growth phase left open only two theoretically possible explanations for the indefinite retention of the capacity to produce bacteriophage by all the individuals in a lineage of lysogenic bacteria. Perhaps a large number of bacteriophage were adsorbed on the bacterial membrane of the first bacterium of the lineage and then buffered and masked from detection in some way, parceled out to each of the daughter bacteria in the lineage during course of cell division. Alternatively, perhaps phage were absorbed into the interior of lysogenic bacteria and transformed into a non-virulent form, distinct from infectious bacteriophage particles that was integrated somehow into the heredity of the host.

By the beginning of October, Lwoff and Gutmann had shown that only the second hypothesis was consistent with the experimental results (Lwoff and Gutmann, 1949b). For this purpose, they cultivated single bacteria isolated in microdrops. At each cell division, one of the daughter bacteria was reisolated, the other was available to produce

more offspring or be employed in various tests. This process was carried on for 19 successive generations. The experimenters carefully ensured that no bacteriophage particles existed inside the bacteria, and that none were contained in, or introduced into, the culture medium. These precautions meant that if adsorbed bacteriophage were to account for the retention of the lysogenic power in bacteria of the 19th generation, each bacterium along the way would have had to obtain (and retain) at least one safely encapsulated infectious phage particle during those 19 generations. Accordingly, the original parent would have had to adsorb $2 \times 10^{19} = 524{,}288$ bacteriophages, which was an obvious impossibility (Lwoff and Gutmann, 1949c). Thus, (1) lysogenic bacteria had to have an inherited endogenous means of producing bacteriophage and (2) the hypothesis that the transmission of bacteriophage in lysogenic strains occurred in the external culture could be safely rejected (Lwoff and Gutmann, 1949c, pp. 790–791). In short, the ability of lysogenic strains to produce bacteriophage was explained by "endomicrobial perpetuation", as Eugène Wollman had predicted.

The question of how phage are liberated was, however, more difficult. At first, Lwoff did not completely reject the possibility that a bacterium could secrete phage without itself being lysed.[16] Part of the problem was due to the existence of two types of bacterial lysis, one of which was slow and left an easily observable bacterial "phantom" behind, the other instantaneous. Slow lysis never produced any bacteriophage. The other form of lysis took less than a second and could only be recognized with constant and sustained observation. Here again only close observation of single bacteria with a microscope allowed the problem to be solved (Lwoff and Gutmann, 1950, p. 727). From this point on, it was clear that fast lysis of a single lysogenic bacterium allowed the liberation of numerous viral particles (Lwoff and Gutmann, 1950, p. 729).[17]

In addition, observation of small chains of bacteria revealed that lysis with production of phage, when it occurred, often affected a significant proportion of the lysogenic bacteria simultaneously. It seemed "obvious that there was *induction* of the production of phage" (Lwoff, 1988, p.

[16] This hypothesis had been proposed by others, e.g., Northrop (1939). Lwoff and Gutmann (1950, pp. 712, 729–731) provide additional references to early authors who accepted this hypothesis, argue for its implausibility, and insist that by 1950 no case of 'secretion' of phage without lysis of the host cell had yet been reliably verified.

[17] At p. 729, Lwoff and Gutmann list the results of several experiments in which they recorded the number of detected bacteriophage released by the lysis of one or a few lysogenic bacteria. The lowest number of phage released was 9, the largest number was 178, and the average for this group of experiments was about 72 phage per bacterium.

77). The occurrence of lysis thus seemed to be a consequence of environmental circumstances, so the task of clarifying what triggered or determined the production of phage became the next order of business. For this purpose, Lwoff initiated a collaboration with Lou Siminovitch and Niels Kjelgaard. Since studying the stimulus that triggered the production of phage could benefit from a statistical investigation, the experimental methodology was reversed, with a return to mass culture, which was part of the reason for seeking new collaborators. For an entire month Lwoff and his collaborators experienced frustration; none of the biochemicals that they tried yielded induction. As is well known, it was partly from vexation – and after the temporary defection of his two colleagues – that Lwoff finally decided to irradiate the strains of lysogenic bacteria with an ultraviolet lamp. The unanticipated success of this series of experiments remained for Lwoff the "greatest thrill – molecular thrill – of [his] scientific career" (Lwoff, 1966, p. 93).

Next Lwoff and colleagues used non-lysogenic control strains to demonstrate that UV-induced lysis was not the direct consequence of the radiation (Lwoff et al., 1950a, p. 841); that all the lysogenic bacteria of a population were capable of liberating phage (work with microdrops) (*ibid*., p. 838); and that the inductive action of ultraviolet was conditional on the *aptitude* of bacterial populations (affected by a certain favorable metabolic state) (*ibid*., pp. 844–847). The question of the control of the aptitude of bacteria to undergo induction became a priority for Lwoff's group during the following months; they made many efforts to understand what made bacteria apt for induction by different sorts of agents (Lwoff, 1951). The presence of bivalent cations such as copper was finally identified as a necessary and sufficient cause (Lwoff, 1952), and the entire line of research on the factors relevant to the occurrence of induction suggested that aptness was the consequence of a perturbation of bacterial metabolism.

By then, it was possible to schematize the entire life cycle of a phage, a virus that changed its form in the course of its life cycle (see section "Beyond Lamarckism: Constructing the Molecular Definition of Virus"). As Eugène Wollman had imagined, lysogeny was a trait that belonged to an individual bacterium and not simply to a bacterial culture. From that point on, lysogeny was a clearly defined state, the reality of which was certified by a convincing body of experimental results. In 1953, in light of the results acquired in Lwoff's Service of Microbial Physiology at the Pasteur Institute, Lwoff and Siminovitch, together with François Jacob and Élie Wollman (after his return from CalTech) redefined the terms pertaining to lysogeny (Jacob et al., 1953). In this

paper, they insisted that lysogenic bacteria are capable of perpetuating the ability to produce phage hereditarily. Lysogeny was thus a property of individual bacteria.

Beyond Lamarckism: Constructing the Molecular Definition of Virus

Shortly after completing these key experiments, Lwoff and his collaborators considered it necessary to develop new concepts to facilitate the interpretation of their experimental results and to explicate the life cycle and properties of phage. It is well known that Lwoff paid special attention to vocabulary and that he was extremely rigorous regarding the choice of terms (Jacob, 1987). For him, a word was the materialization of a concept, and a concept, at least in biology, was, from the outset, a generalization from particular instances. Colligation of disparate facts should count as an important part of the theoretical work of a scientist; in this respect he saw himself as continuing in the steps of William Whewell and Claude Bernard (Lwoff, 1957, pp. 250–251). Furthermore, for Lwoff (as also for Monod and Jacob), words have the function not only of registering the progress of knowledge, but also of provoking new knowledge: by indicating a direction for research to follow and newly formed concepts to guide the continuing research of experimenters (Lwoff, 1966, p. 96).

In this section, we follow Lwoff's efforts to revise and devise terms and concepts bearing on the nature of prophage from 1949 to 1957. For the sake of concision and clarity, we restrict our analysis primarily to Lwoff's development of concepts during this period, although, of course, he was not the only one to contribute to the molecular definition of virus.[18] For our purposes the most important point is to understand the stages of his progress in revising and replacing the notion of particles endowed with genetic continuity. The experimental work, as such, took place from 1949 to 1953. In 1957 Lwoff gave the famous Marjorie Stephenson Memorial Lecture on "The Concept of a Virus" in London (Lwoff, 1957). On that occasion, he reinterpreted and extended the results obtained from studying phage to all viruses and constructed the first molecular definition of a virus.

[18] Among the people Lwoff mentioned in "The concept of a virus" (Lwoff, 1957) are Andrewes and Burnet (Andrewes, 1952; Burnet, 1945 [cited as 1950]) as proponents of treating viruses as organisms, Stanley as a proponent of viruses as being composed simply of [complex] molecules (Stanley, 1952), and Bawden and Pirie as coming closer to his own view that viruses cannot be properly classified as either living or as simply being molecules (Bawden, 1952; Bawden and Pirie, 1951).

Next we examine how the concept of the prophage was progressively ''devitalized'' and ''de-Lamarckianized'' in lockstep with its molecularization. Originally conceived as an entity endowed with genetic continuity, i.e., as an autonomous particle capable of self-reproduction, the prophage eventually became the model from which to rethink both the molecular nature of viruses and their relation to their cellular hosts. In the process, Lwoff (and later Jacob) paid special attention to avoid the term ''inheritance of acquired characters''.

It was partly thanks to the power of the new experimental tools that began to become available in the late 1930s that Lwoff came to reject Lamarckism in the course of work that he conducted with Alice Audureau on the bacterium *Moraxella lwoffii*. They found that succinic acid could only be metabolizedby by this bacterium after a latent period. Through a succession of refined experiments, they showed that the adaptation to the new substrate involved chance mutation and subsequent selection at the population level, and could not be interpreted as resulting from Lamarckian mechanisms such as individual acclimatization and inheritance of acquired characters (Lwoff and Audureau, 1941). Two years before the famous fluctuation test of Salvador Luria and Max Delbrück (Luria and Delbrück, 1943), Lwoff and Audureau reached much the same conclusion regarding the adequacy of genetics and the inadequacy of Lamarckism in microbiology.

This group of projects concerning bacterial mutations facilitated Lwoff's publication of a review article in the *Cold Spring Harbor Symposia on Quantitative Biology* in 1946. In this text Lwoff highlighted the capital findings in the genetics of microorganisms obtained by Luria Delbrück and Beadle, which he recognized as being of fundamental importance (Lwoff, 1946, pp. 149–150). Lwoff used the ensemble of available experimental findings (including his work with Alice Audureau) to put forward an explicit conclusion in favor of a rigorous Darwinian conception of evolution in unicellular parasites, claiming that ''it seems reasonable to assume that this evolution [of parasitic microorganisms] resulted from selection of spontaneous mutants'' (Lwoff, 1946, p. 152). Lwoff's conclusion based on these significant findings help us to understand why he did not retain the explicitly Lamarckian dimension of the corpuscular explanation developed by Eugène and Elisabeth Wollman before WWII in the field of lysogeny.

In the first note on lysogeny, published on 19 September, 1949 (Lwoff and Gutmann, 1949a), Lwoff restated the importance of the results already obtained by the Wollmans. He reported, notably, that in the 1930s they had shown that lysogenic bacteria did not liberate any phage

when they were lysed with lysozyme. This finding supported the view that lysogenic bacteria do not, in general, contain free phage. As we have seen, this led the Wollmans to the idea that viruses have several ''phases'' and that the phase of free, virulent viruses is a separate well-defined phase in the course of their life cycle. From the beginning, Lwoff adopted this conception, parallel in many ways to his account of the phases in the life history of parasitic ciliates. He joined to it the view defended earlier by Burnet and McKie (Burnet and McKie, 1929), who interpreted the lysogenic phase of the virus as a primordium (*Anlage*) that could be incorporated into the heredity of a lysogenic bacterium. The term ''probacteriophage'' appeared for the first time in a note from 20 March 1950, to describe this non-virulent endomicrobial phase (Lwoff et al., 1950b). In December 1950, in a long memoir synthesizing all their results on the determination of induction, Lwoff and his colleagues characterized the probacteriophage as a *particle endowed with genetic continuity* (Lwoff et al., 1950a, p. 817). This connection to the concept of genetic continuity enabled Lwoff to draw on his earlier work in protozoology by utilizing the concepts he had previously constructed regarding the nature and the functioning of the kinetosomes of ciliates in addressing the question of lysogeny (Galperin, 1987).

Lwoff explicitly referred to this conceptual continuity, which he self-consciously employed, in describing his work as early as 1950:

> Nutrition, metabolism, and particles endowed with genetic continuity act conjointly in bacteria that produce bacteriophage. *Kinetosomes, their movements, and the factors that govern their specific activity, have served me as a model and guide for dealing with lysogenic bacteria.*
>
> I was thus prepared to find that lysogenic bacteria live in equilibrium with a particle endowed with genetic continuity, a ''probacteriophage'' – not infectious and not pathogenic – and that this equilibrium could be disrupted by perturbations of the microbial metabolism, by an inductive shock acting on the bacteria provided with a particular nutritional regime. (Lwoff, 1950b, p. 17, emphasis added)

At this point, it was expected that the virus would be homologous to a particle with genetic continuity. By the end of 1950, a difficult question remained unanswered, namely, what was the nature of the viral unit that possessed genetic continuity? Was it the entire virus or one of its components? In other words, to what extent was the prophage different from the virulent form? It is clear that in 1952 Lwoff still held that the

prophage (a term that was progressively substituted for ''probacteriophage'' in 1951 and 1952) was probably a morphologically defined particle, capable of perpetuating the capacity of producing the lethal particles (bacteriophage) that are part of the virus life cycle.

After returning from the US at the beginning of 1952, Élie Wollman, like Esther and Joshua Lederberg, worked on the problem of genetic determination of lysogeny (Galperin, 1987, pp. 219–220). At the time, the Lederbergs held that phage could serve as a model system for the study of cytoplasmic inheritance (Lederberg and Lederberg, 1953). Wollman summarized the possible hypotheses concerning the nature of prophage with four different models (Galperin, 1987, p. 221). One of these models treated prophage as a gene ''intimately linked to the genetic material of the bacteria, with which it interacts interdependently during duplication'' (Wollman, 1953, p. 282).

The results that Alfred Hershey and Martha Chase published at this time helped to distinguish among these different possibilities (Hershey and Chase, 1952). In demonstrating that only the DNA of a virulent phage was necessary for its reproduction inside a sensitive (i.e., nonlysogenic) bacterium, Hershey and Chase showed which viral structure is responsible for genetic continuity. For Lwoff, DNA ''may well be the substrate of the genetic continuity of phage, for which it serves, in some way, as the germinal material [germe]'' (Lwoff, 1953a, p. 235). This restriction led quite naturally to retention of the model of prophage as a gene linked to the bacterial chromosome, a commitment that shows that, at this point, ''genetic continuity'' was beginning to merge with ''genetic'' in the geneticists' sense. Lwoff proposed in addition that the prophage was attached into a specific site on the bacterial chromosome. Lysogeny – and the genetic continuity of the lysogenic trait in lysogenic bacteria – would then be the consequence of the conjoint replication of the bacterial genes and the viral genes. Inductive agents, by perturbing the bacterial metabolism, broke the link between the prophage and the bacterial chromosome, thereby leading to the production of infectious particles (*ibid*., pp. 235–237). In 1953, in his celebrated review of lysogeny, Lwoff provided a revised version of his concept of the prophage:

> This specific noninfectious structure, endowed with genetic continuity, is called prophage. Prophage is the form in which lysogenic bacteria perpetuate the power to produce phage. Its multiplication is correlated with bacterial reproduction. It seems to be located at a specific site of a bacterial chromosome and to behave in crosses as a bacterial gene. (Lwoff, 1953b, p. 272)

A few lines later, Lwoff clarified the point that a prophage should be seen as an ensemble of *several* genes. Lysogeny thus consists of the viral *genome* linked to the bacterial *genome*. Now clearly laid out, the concept of the prophage permitted simultaneous explanation of lysogeny and induction.

He then left it to others to pursue the characteristics of the prophage, especially to Francois Jacob who entered Lwoff's service in September 1950. As a PhD student, Jacob worked intensively on lysogeny from 1950 to 1954. It is striking to observe how often he utilized paraphrases in order to avoid the use of the phrase "inheritance of acquired characters". In his doctoral thesis, published in 1954 under the title *Les bactéries lysogènes et la notion de provirus* (*Lysogenic bacteria and the notion of provirus*), Jacob took advantage on several occasions of the concept of genetic continuity (Jacob, 1954, p. 1, p. 14, pp. 18–19). Much like Lwoff, however, and in contrast to Eugène Wollman, he managed to avoid Lamarckian formulations of the process of lysogeny wherever possible. For example:

> If we admit the hypothesis that the prophage is indeed the genetic material of the phage incorporated into the bacterial genetic material, the lysogenization of a bacterium corresponds to the *acquisition* by infection of a *hereditary character* […]. (*ibid.*, pp. 139–140, emphasis added)

The concepts *inheritance*, *acquired* and *character* are all roughly there, but they are put together in a way that does not sound Lamarckian. The explanation is indeed entirely based on genetic concepts, thus providing the tools for explaining away the appearance of Lamarckian inheritance.

At this point the desire of the French Pasteurians to avoid any sort of Lamarckian description of lysogeny cannot be fully understood without taking Lysenkoism into account. Given that Monod was much more directly involved the "Lysenko affair" than Lwoff or Jacob, we will take up this significant political and ideological issue in our companion article on enzymatic adaptation. Nevertheless, it is already worth noting that, according to Jacob, "to do genetics was […] to insist on substituting reason for intolerance and fanaticism" (Jacob, 1998, p. 32). Lysenkoism thus strengthened Lwoff and Jacob's motivation to prevent any Lamarckian use of their work and forced them to rule out any ambiguous statements. A molecular understanding of the concept of a virus, free from its Lamarckian and vitalistic origins finally emerged from this meticulous theoretical and lexical work.

At the end of his 1953 review of lysogeny, Lwoff sketched, for the first time, a general molecular definition of a virus based on the results of his studies of bacteriophage. This lengthy and dense text (68 pages) concludes with an appendix comprised of a series of six notes. The last of these, entitled "6. *Is a bacteriophage a virus? What is a virus*?", argues for the relevance of phage to defining viruses and ends with a tentative definition of a virus. Lwoff proposed three criteria in this section in order to achieve an unambiguous distinction between phage on the one hand and cells and protists on the other: (1) unlike cells and protists, phage have only one type of nucleic acid; (2) cells and protists "are reproduced essentially from the integrated sum of their constituents," while "bacteriophage is produced or reproduced from its nucleic acid (case of T2) or from prophage (case of lysogenic bacteria)"; and (3) unlike cells, phage cannot reproduce by direct division and cannot reproduce when they have the form of an organized bacteriophage particle (Lwoff, 1953b, p. 332). Lwoff concluded his text programmatically:

> Perhaps a discrimination between viruses and nonviruses could be attempted on this basis. If this difference between viruses and nonviruses would be found to be justified and generalizable, then the term virus shall acquire, at last, a definite meaning. (*idem*.)

This first attempt at a definition is remarkable in at least two respects. On the one hand, it presents the basis for Lwoff's final attempt to clarify this concept, completed in 1957. On the other hand, it ratifies changes in his beliefs regarding two core concepts, namely, the concept of a virus and the more general concept of an entity that has genetic continuity.

In effect, by firmly establishing that viruses – or at least phage – could not *directly* produce new equivalent entities, Lwoff denied their former status of particles endowed with *direct* genetic continuity [even if they remain entities endowed with indirect genetic continuity through their DNA molecules (see section "How to Break with Lamarckism? Particulate Heredity, Genetic Continuity and the "Molecularization" of Virus (1949–1957)")]. Contrary to the kinetosomes of ciliates the virulent particles of bacteriophage are produced *de novo* in each phage life cycle. Lwoff is explicit about this point: "Bacteriophage particles are never produced directly by division of a pre-existing phage particle but by organization of non-phage material" (Lwoff, 1953b, p. 332, see also Lwoff, 1957, p. 243).

This conceptual shift marks the last in a long chain of intellectual steps taken by Lwoff. In 1932, he considered particles endowed with

genetic continuity (including bacteriophage) to be genuine intracellular living organisms in the cytoplasm, autonomous and capable of growth and self-reproduction (Lwoff, 1932). The concept of prophage weakened the force of genetic continuity when it became clear in the 1950s that prophage, as such, did not have the power of self-reproduction. In phage, as in viruses, only ''genetic material'' appeared in fact to exhibit ''genetic continuity'' – and, even then, genetic material required cellular apparatus for its reproduction. By 1957, Lwoff finished the process of ''molecularization'' by indicating that the prophage carries the ''information'' required for the synthesis of virulent viral particles (Lwoff, 1957, p. 241). In the same text, he added a fourth distinguishing criterion peculiar to viruses: they do not have a system for the production of chemical energy (*ibid.*, p. 242), which made viral particles into obligate intracellular parasites that are definitively inert in their own right. For him, there was no longer any doubt, viruses are a category apart: they were not endowed with direct genetic continuity (though they had a kind of indirect genetic continuity), nor did they count as living beings (*ibid.*, p. 248). In the space of twenty-five years, viruses had thus lost two of the characteristics formerly considered essential in their characterization. Viruses had become molecular machines with their own discriminating characteristics. Lwoff's celebrated formulation makes the point: ''viruses should be considered as viruses because viruses are viruses'' (*ibid.*, p. 252).

Conclusion

In this study we have demonstrated that Lamarckism or, more precisely, the concept of inheritance of acquired characters, was essential in shaping the debates surrounding bacteriophagy and lysogeny in the Pasteur Institute from 1917 to 1957. We have shown that two conceptions of heredity were at stake inside the Lamarckian framework: a physiological-protoplasmic conception versus a morphological-particulate one. The physiological conception stated that biological inheritance was only the transgenerational continuation of individual physiology – whether normal or pathological. This Bernardian understanding was typical of the French neo-Lamarckism that was prevalent at the beginning of the twentieth century. It was still of central importance to Pasteurians like Félix d'Hérelle and especially Jules Bordet who developed the explanation of ''hereditary nutritive vitiation'' during the 1920s. In contrast, Eugène Wollman opposed a more particulate conception of

bacteriophagy and lysogeny based on the idea that the bacterial virus was something like an autonomous gene. During the 1930s, Eugène and Elisabeth Wollman marshaled substantial evidence in support of this theoretical claim. After WWII and the death of the Wollmans, André Lwoff met the challenge of completing his friend's research program. The fundamental results obtained by Lwoff and his group paved the way to the first molecular definition of virus, put forward in 1953 and completed in 1957. In the process, Lwoff purged the concepts of prophage and virus of any Lamarckian commitments. By the late 1940s and early 1950s, Lamarckism had become an obstacle to be overcome for people like André Lwoff and François Jacob. This epistemological posture was also strongly reinforced by the development of Lysenkoism in the USSR but also in the specific French context of the post-war period (cf. the second article of this pair, now in progress).

Thus, Lamarckism played a complex dual role in the setting-up of the French school of molecular biology. In the case of lysogeny, our intention was to understand the subtle and progressive transformation of the Lamarckian program of the Wollmans as it was moved into the molecular domain in ways that were shaped – and later endorsed – by Lwoff. This transformation never amounted to a definitive rupture, and Lwoff remained faithful to the idea that the lysogenic power was reified in a discrete morphological factor, namely the prophage. In a sense, in order to enter genuinely into the era of genetics, this tradition had to free itself from the holistic and delicately Bernardian and Lamarckian intellectual atmosphere embodied in d'Hérelle's and especially Bordet's declarations. But in another sense, it was crucial for this tradition to come as close as possible to a *physiological* interpretation of the genetic categories.

In our forthcoming article, we will apply the same interpretative schema to the history of the concept of enzymatic adaptation in the Pasteur Institute. Originally, the phenomena in question received a Lamarckian explanation, but that explanation was later replaced by a strict genetic and molecular one. In particular, we will examine in detail the birth of the concept of ''cellular memory'' during the 1950s in the work of Jacques Monod and Melvin Cohn. This concept was at the crossroads of two main historical lines. On the one hand, it was supposed to ratify the defeat of traditional Lamarckism. On the other, it can be argued that a model of cellular memory, well supported by experimental results, ought to count as a model of non-genetic, or, more specifically, epigenetic inheritance. Since at present some biologists consider epigenetic inheritance to have vindicated a form of inheritance of acquired

characters, our next article will examine the ironic possibility that the very research that set aside Pasteurian Lamarckism contained the seeds of a vindication of the inheritance of acquired characters.

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