Series

What history tells us
III. André Lwoff: From protozoology to molecular definition of viruses

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1. Introduction

The ideas of the historian Thomas S Kuhn on the development of science have pervaded contemporary scientific thought. It is widely admitted that there is, in the history of scientific disciplines, an alternance of normal science – with a dominant paradigm – and revolutionary episodes, corresponding to the replacement of an 'old' paradigm by a new one. The rise of molecular biology is frequently identified with a Kuhnian revolution. However, many doubts have been voiced concerning the value of the Kuhnian model, in particular the possibility of applying it beyond the discipline in which it was elaborated – i.e. physics (Wilkins 1996). Did the molecular paradigm replace a previous paradigm, or simply fill a 'hole' in the preexisting explanations? Is the new vision incommensurable with the previous one, as successive paradigms are supposed to be?

One way to approach the nature of the transformations occurring in science is to study the work of scientists who participated in them before, during, and after the 'revolutionary' event. Such a precise study frequently highlights continuities more than the discontinuities. André Lwoff is an outstanding example of those scientists – biologists – who built a bridge between 19th century knowledge and biology as it is at this initial phase of the 21st century. In this series, we have already mentioned André Lwoff as the head of the laboratory in which François Jacob and Jacques Monod elaborated the operon model (Morange 2005). More precisely, in his laboratory André Lwoff was at the origin of two lines of research, on enzymatic adaptation and lysogeny, the convergence of which generated the operon model. We will describe the different phases of Lwoff's work, outline some of its features, and underline the continuities behind its apparently eclectic nature (Lwoff 1971; Burian and Gayon 1991, 1999).

2. Schematic description of André Lwoff's scientific work

André Lwoff successively made essential contributions in four different fields of research. He was attracted to biology and the Pasteur Institute by the great immunologist Elie Metchnikoff, a friend of his father. His first scientific work was carried out in the years 1920 to 1930 at the Marine Biological Laboratory at Roscoff in Brittany under the supervision of Edouard Chatton, the famous protozoologist who drew the distinction between prokaryotes and eukaryotes. The work was pursued for twenty years at the Pasteur Institute in Paris, in the Department headed by Félix Mesnil. This work was two-sided: the first objective was to characterize the diversity of protists – Lwoff described many new species – and of their morphologies; the second objective was to find conditions to maintain pure cultures of these organisms, and in particular of trypanosomides, for medical purposes. The main result of Lwoff was his demonstration of the importance of the cortex of the ciliates in their morphogenesis, and the characterization of the kinetosomes, structures that give rise to the cilia, as particles endowed with hereditary continuity. Lwoff's interest in ciliates persisted throughout his life: in 1950, he published a book entitled *Problems of morphogenesis in ciliates* (Lwoff 1950) and his last two scientific publications, at the age of 88, were devoted to the organization of the cortex in ciliates (Lwoff 1990a and 1990b). Ciliates played a complex – and ambiguous – role in the development of new ideas in biology in the 20th century (Sapp 1987): we will return to this tortuous history in a forthcoming article.

The need to keep cultures of these organisms 'pure' naturally led Lwoff to the characterization of growth factors for these organisms, and then for bacteria. He acquired the necessary knowledge of biochemistry in Otto Meyerhof's laboratory in Heidelberg in 1932, and in 1936, in Cambridge, in David Keilin's lab. André Lwoff contributed to the characterization of two growth factors, factor X or hematin, and factor V More importantly, he provided the correct interpretation for the role of growth factors. They were not acting as energy sources or simply as catalysts, but were components of the enzymatic machinery in charge of the metabolism. They became essential because the organisms are no longer able to synthesize them. The general character of this "loss of function", which presumably took place during the course of evolution, was underlined in a book published in French in 1944 with the title *L'évolution physiologique*. *Etude des pertes de fonction chez les micro-organismes* (*Physiological evolution: study of the loss of function in microorganisms*). Due to the prevailing historical circumstances, this book did not attract a lot of attention from other scientists (Lwoff 1944).

The third field of research was the study of lysogeny. Lwoff had observed with attention the studies on bacteriophage by Félix d'Herelle and, during the inter-war period, those of Eugène and Elisabeth Wollman on lysogeny. The Wollmans were both deported in 1943 and died in a concentration camp. Lwoff took it as a personal challenge to demonstrate the importance of the observations made by the Wollmans to the hitherto sceptical American phage group (Lwoff 1966). He provided only two, but nonetheless decisive, observations of the system. By micro-manipulation, he was able to observe that lysogenic bacteria did not normally release any bacteriophage, but that, from time to time, they "spontaneously" lysed, releasing many copies of the bacteriophage; most of all, he found a reproducible way to induce the synthesis of bacteriophages in a lysogenic strain (Lwoff *et al* 1950).

After writing a review in 1953 in which he expressed the problem of lysogeny in a modern way, and pointed out the value of such a system in shedding some light on human diseases such as cancer (Lwoff 1953), he left this subject in the very competent hands of Elie Wollman and François Jacob. Thereafter, with the help of the American National Foundation for Infantile Paralysis, he turned to his fourth field of research, the study of polioviruses, More than the observations he made on the development of this virus and its sensitivity to heat, his major contribution was the clarification of the concept of virus, and the efforts he made to introduce a stable classification and nomenclature (Lwoff 1967). Introduced first in his 1953 review on lysogeny, the definition was made more precise in the Marjorie Stephenson lecture of 1957 (Lwoff 1957). To the criteria of size and conditions of growth Lwoff substituted or added molecular criteria, such as the nature and number of nucleic acids.

3. Some characteristics of this eclectic opus

It is obvious that André Lwoff made a decisive contribution to the molecular transformation of biology in at least three of the fields in which he worked. His contributions on the growth factors were fundamental in showing the ubiquity of the biochemical reactions operating in organisms, a firm basis on which molecular biologists supported their conviction that there are biological principles of organization common to all organisms (Smocovitis 1992). Lwoff replaced a traditional definition of viruses by a molecular one, and through this process explained what a virus is. His contribution to lysogeny was decisive for the future work of Jacob and Wollman. Bringing together the two lines of research that underpinned the operon model was the result of a conscious feeling that these two fields of research had something in common – as he explicitly suggested as early as 1936 (Lwoff 1936). In addition, Lwoff was among the first to present the new results of molecular biology to the lay reader (Lwoff 1962).

This obvious contribution of André Lwoff to the molecularization of biology did not prevent him from being fully embedded in the research traditions of the 19th century. Historians have suggested that this tradition was 'Bernardian' (Burian and Gayon 1991), i.e. inspired by the work of Claude Bernard, with a strong emphasis put on the physico-chemical characterization of organisms. We think that this influence of 19th century ideas was more general. For instance, the second law of thermodynamics and the apparent general movement towards disorder, contradicted by the evolution of organisms towards complexity – a subject of lively debate in the second part of the 19th century and at the beginning of the 20th century – still haunts both Lwoff's 1944 work *L'évolution physiologique*, and the 1962 book *Biological Order*. The constant influence of the environment on organisms means that the second law permeates them. Personally and institutionally, Lwoff was a Pasteurian, deeply attached to the traditions of the institute. Félix Mesnil, in whose Department he entered at the age of 19, had been the private secretary of Louis Pasteur. The study of microorganisms, "from protists to phages", was a characteristic of the Pasteur Institute; and until his death, Lwoff remained a strong supporter of the independence and preservation of this tradition (Lwoff 1981).

What best characterizes André Lwoff, more than these revolutionary and conservative facets, is the permanence of a “heterodox spirit” (Peyrieras and Morange 2002). Lwoff was ready to question every theory and model, whatever its position and influence. In the landscape of French biology in the first part of the 20th century, in which Lamarckian ideas had deeply penetrated, Lwoff described himself as a strict Darwinian, and opposed Lamarckian ideas with energy. This did not prevent him, however, from reporting an example of inheritance of an acquired trait in one of his last publications (Lwoff 1990a).

Lwoff was a strong supporter of the genetic approach to biological phenomena – once again isolated in the French biological landscape – but was ready to challenge the “nuclear monopoly” and to support the hypothesis of the existence of forms of genetic continuity in the cytoplasm (Lwoff and Ephrussi 1949). In 1946, by his analysis of spontaneous biochemical mutations in bacteria, he clearly challenged the simple one gene–one enzyme relation established a few years before by George Beadle and Edward Tatum (Lwoff 1946): he showed that single mutations could have pleiotropic effects, i.e. simultaneously alter different biochemical characteristics of the organisms. The attitude of Lwoff can best be explained by his intimate conviction that scientific models and theories are not dogma, and that the most interesting phenomena are precisely those which are at the border, those that present theories are unable to explain – when, for instance, genes have to cope with the environment.

4. Conclusion

Independently of what one may consider retrospectively as forward-looking or past ideas, three features characterize the whole scientific life of André Lwoff. The first is his huge biological culture. This explains how he was so rapidly able to be productive in fields apparently new to him, such as lysogeny and virology. It also allowed him to be a very efficient guide for his collaborators. For instance, he saw, before Jacques Monod himself, that the phenomenon of diauxy observed by Monod – the apparent transitory preference for one of two nutrient sources – was a consequence of the involvement of adaptive enzymes in the transformation of the neglected nutritive source (Monod 1966). He guessed very early that the control of lysogeny and enzymatic adaptation had something in common. His culture was not limited to biology: André Lwoff was a humanist (Lwoff 1981).

The second feature is Lwoff’s permanent, obsessive attention to the precision of thought and language, the latter being a requirement for the former. This deeply impressed his collaborators, including Monod and Jacob, and probably explains in part the quality of their very different styles. Both showed the same attention to the words they chose and to the clarity of thought. But Monod’s style was more lyric, whereas Jacob’s was more dry. The need to use the right word in the right place sometimes led to the simple conclusion that the right word . . . did not exist. Hence the formation of a committee of terminology headed by Lwoff in the laboratory, in charge of the creation of these new words (Jacob *et al* 1953). The consequence was that many words which entered molecular biology at that period – prophage, virion, capsid, etc. – were created by Lwoff and his collaborators.

Finally, Lwoff was a free spirit, deeply attached to rationality. As we have seen, this meant that he never considered scientific hypotheses as dogma, and he also defended science and scientists whenever they were threatened by one or other ideology. Such was the case in the Lysenko affair when in 1948 scientists belonging to the communist parties of Western countries were abruptly asked to reject genetics (Lwoff 1981). Lwoff had never been a member of the communist party, and was not personally involved. But he considered as necessary to fight against what he called “the communist mysticism” and the “surrender of reason” by writing an article in the French newspaper *Combat*. By his writings and actions, he was also a strong opponent to any form of antisemitism all his life.

Lwoff was both a precursor of the molecularization of biology, and a man of the 19th century. He was a very rich personality, full of contrasts.

References

Burian R M and Gayon J 1991 Un évolutionniste bernardien à l’Institut Pasteur? Morphologie des ciliés et évolution physiologique dans l’oeuvre d’André Lwoff; in *L’Institut Pasteur: Contributions à son histoire* (ed.) M Morange (Paris: La Découverte) pp 165–186

Burian R M and Gayon J 1999 The French school of genetics: from physiological and population genetics to regulatory molecular genetics; *Annu. Rev. Genet.* **33** 313–349

Jacob F, Lwoff A, Siminovitch A and Wollman E 1953 Définitions de quelques termes relatifs à la lysogénie; *Ann. Inst. Pasteur* **84** 222–224

Lwoff A 1936 Remarques sur une propriété commune aux gènes, aux principes lysogènes et aux virus des mosaïques; *Ann. Inst. Pasteur* **56** 165–170

Lwoff A 1944 *L’évolution physiologique. Etude des pertes de fonctions chez les microorganismes* (Paris: Hermann)

Lwoff A 1946 Some problems connected with spontaneous biochemical mutations in bacteria; *Cold Spring Harbor Symp. Quant. Biol.* **11** 139–155

Lwoff A 1950 *Problems of morphogenesis in ciliates. The kinetosomes in development, reproduction and evolution* (New York: John Wiley)

Lwoff A 1953 Lysogeny; *Bacteriol. Rev.* **17** 269–337

Lwoff A 1957 The concept of virus; *J. Gen. Microbiol.* **17** 239–253

Lwoff A 1962 *Biological order* (Cambridge: MIT Press)

Lwoff A 1966 The prophage and I; in *Phage and the origins of* *molecular biology* (eds) J Cairns, G S Stent and J D Watson (New York: Cold Spring Harbor Laboratory Press) pp 88–99

Lwoff A 1967 Principles of classification and nomenclature of viruses; *Nature* (*London*) **215** 13–14

Lwoff A 1971 From protozoa to bacteria and viruses: Fifty years with microbes; *Annu. Rev. Microbiol.* **25** 1–26

Lwoff A 1981 *Jeux et combats* (Paris: Fayard) pp 1–281

Lwoff A 1990a L'organisation du cortex chez les ciliés: un exemple d'hérédité des caractères acquis; *C.R. Acad Sci. Paris III* **310** 109–111

Lwoff A 1990b Changements de structure et d'organisation des mailles du réseau cortical des ciliés *et al* lostérie; *C.R. Acad. Sci. Paris III* **311** 133–135

Lwoff A and Ephrussi B (eds) 1949 *Unités biologiques douées de continuité génétique* (Paris: Cen. Natl. Rech. Sci.)

Lwoff A, Siminovitch L and Kjelgaard N 1950 Induction de la lyse bactériophagique de la totalité d'une population microbienne; *C.R. Acad. Sci. Paris* **231** 190–191

Monod J 1966 From enzymatic adaptation to allosteric transitions; *Science* **154** 475–483

Morange M 2005 What history tells us I. The operon model and its legacy; *J. Biosci.* **30** 313–316

Peyrieras N and Morange M 2002 The study of lysogeny at the Pasteur Institute (1950–1960): an epistemologically open system; *Stud. Hist. Philos. Biol. Biomed. Sci.* **33** 505–516

Sapp J 1987 *Beyond the gene: cytoplasmic inheritance and the struggle for authority in genetics* (Oxford: Oxford University Press) pp 1–266

Smocovitis V B 1992 Unifying biology: the evolutionary synthesis and evolutionary biology; *J. Hist. Biol.* **25** 1–65

Wilkins AS 1996 Are there 'Kuhnian' revolutions in biology?; *BioEssays* **18** 695–696

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