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Giant viruses: The difficult breaking of multiple epistemological barriers☆

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ABSTRACT

The discovery of the first "giant virus", Mimivirus, in 2003 could solely have been that of an exceptional freak, a blind alley of evolution as occasionally encountered in biology, albeit without conceptual significance. On the contrary, once broken this epistemological barrier, additional unrelated families of giant viruses such as the Pandoraviruses, the Pithoviruses and most recently Mollivirus, were quickly unraveled, suggesting that an entire chapter of microbiology had been ignored since Pasteur and Ivanovski. In this article, we examine to what extent the giant viruses challenge previous definitions of viruses, the diversity of forms they could take, and how they might have evolved from extinct ancestral cellular lineages. Inspired by the epistemology of Gaston Bachelard, we will also suggest the reasons for which giant viruses laid hidden in plain sight for more than a century. Finally, we propose a new definition for "viruses" that paradoxically emphasize the fact that they do not encode a single universally shared macromolecule or biochemical function.

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1. Introduction: Giant viruses were not meant to be discovered by virologists

The recent discovery of a whole diversity of giant viruses in quick succession (Arslan, Legendre, Seltzer, Abergel, & Claverie, 2011; Legendre et al., 2014, 2015; Philippe et al., 2013; Raoult et al., 2004) demonstrated that biology is still a scientific area where some of the most established concepts might be proven wrong, or seriously misleading, even though there were not challenged for more than a century. It also reminded us of the danger of solely envisioning (and funding) biological research in the context of biomedical, economical or societal challenges. The giant viruses that we know today do not cause any harm to humans or animals, and do not destroy crops, the three main incentives that guided the development of virology (Helvoort, 1996) since its very beginning with the isolation of the Tobacco mosaic disease virus (Ivanovski, 1892). Such utilitarian attitude was actually reinforced by a basic technical reason: studying viral diseases provided the researchers both with the virus and its host at once, a *sine qua non* condition to study and propagate such obligatory parasites unable to multiply outside specific cells. Ironically, soon after the serendipitous discovery of the first - totally innocuous- giant virus, it has become clear that their marine relatives played an essential role in regulating the populations of unicellular plankton the equilibrium of which depends on half of the oxygen production and carbon

☆ This article challenges the traditional notion of "virus". In order to describe how this notion should be changed in the light of recent discoveries, we needed to start from the traditional sense of the word, as accepted by most contemporary biologists. For the majority of them, "virus" designates the inert infectious particle which uses the biosynthetic capacity of the cell it infects to multiply. Instead, we will propose that the essence of a virus is the intracellular process akin to the development of a transient microorganism. There is therefore an unavoidable ambiguity each time the word "virus" is used in this article, depending on whether we are meaning the "particle", or the whole process. For instance, given the central role that the small size of viruses played in the history (and the methods) of virology, "giant virus" is definitely an oxymoron in the traditional meaning of the word. The same expression is devoid of sense when using our own new definition.

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sequestration on our planet (Fischer, Allen, Wilson, & Suttle, 2010; Weitz et al., 2015), one of the most pressing societal challenge of our time.

Following a quick historical account of the discovery of giant viruses and a description of their unusual properties, we will examine the well-accepted views that they appear to challenge. We will more specifically develop three main topics: the new notion that viruses exhibit a gradation in their "absolute" parasitism, the increasingly blurred frontier between the viral and cellular worlds, and how viruses might have evolved to their present diversity. Along the text, we will point out the various kinds of epistemological obstacles (*sensu* Bachelard) that precluded the discovery and the recognition of the viral nature of giant viruses. Finally, we will propose a new definition for "viruses" that we hope (but do not really expect) could stand the test of time and remain applicable to the increasingly exotic types of microorganisms that remain to be discovered.

2. The traditional concept of virus

2.1. "Virus" as a failed microbe

The germ theory of diseases often hailed as the most important work of Louis Pasteur (although initiated by Lister and refined by Koch) paradoxically set up the stage for the discovery of viruses. In front of the French Academy of Medicine, Pasteur proposed in 1878 that infectious diseases were caused by the proliferation of specific – living – microorganisms, visible under the light microscope and cultivable on a nutritious broth (Pasteur, 1878a,b; Pasteur et al. 1878). Few years later Charles Chamberland designed a porcelain filter capable of retaining these microbes, thus providing the first straightforward experimental protocol to rapidly demonstrate the microbial nature of any infectious agent (Chamberland, 1884). Ironically, the year of Pasteur's Jubilee (1892) celebrating his lifelong accomplishments, Dimitry Ivanovski, a young Russian botanist at the beginning of his career, poked the first hole in the newly established paradigm by showing that the agent transmitting the highly contagious Tobacco mosaic disease was not retained by the Chamberland filter, neither could be seen under the microscope, nor could it be cultivated in traditional growth media (Ivanovski, 1892).

Retrospectively, it was very fortunate that this unambiguous falsification (*sensu* Karl Popper) of the barely established theory of Louis Pasteur did not resurrect the fallacious miasma theory which states that contagious diseases are communicated by corrupted air. Instead, following the confirmation of Ivanovski's experiment by Martinus Beijerinck (Beijerinck, 1898), the unexpected filterability of the tobacco mosaic disease agent triggered the emergence of the concept of "virus" as qualitatively different from the usual microbes (i.e. bacteria). Yet, Beijerinck's definition of the new "virus" as a non-corpuscular living fluid ("contagium vivum fluidum") was more of a regression than a progress, uncomfortably close to the antique acceptance of the word "virus" designating anything from stench, poison, or a viscous secretion. Following this nebulous start, the notion of "filterable virus" remained enigmatic until the first electron microscope images of Tobacco mosaic viruses (TMV) were produced in 1939 (Kausche, Pfankuch, & Ruska, 1939).

2.2. Awaiting for the "modern" definition of viruses

Beijerinck's views were so opposed to the prevalent ideas of the time that they did not receive much attention. Already in 1903, Roux challenged the "fluid contagiosum" hypothesis by dubbing it "very original", and considered these filterable agents as not different from the tiny mycoplasma cells he just discovered (Roux, 1903). However, Chamberland's filtering protocol led to the rapid discovery of many other "filterable" viruses. By 1931, nearly two dozen diseases had already been associated with viruses, including yellow fever, rabies, fowl pox, and foot-and-mouth disease in cattle (reviewed in Helvoort, 1996). Yet, the nature of these "filterable viruses" remained elusive, with competing hypotheses ranging from replicating molecules (proteins) to small intracellular parasitic bacteria such as Rickettsia. Until 1950, viruses continued to be defined by three negative properties: they were invisible under the light microscope, they were uncultivable in absence of living cells, and they were not retained by Chamberland's filter (on the use of filtration as a criterion for being a virus and on the related "negative" definition of viruses, see Méthot, 2016). Later in that period, it was realized that viruses did not multiply by binary fission, and that their multiplication within the infected cell was preceded by an "eclipse" phase, during which traces of them were no longer visible. This apparent lack of "organismal" continuity, as well as the - epistemologically unfortunate - crystallization of TMV by Wendell Stanley in 1935 (whom received the 1946 Nobel Prize in Chemistry – not Physiology/Medicine- for his work) weighted a lot in relegating the viruses outside of mainstream microbiology as far as considering them outside of the living world, an opinion still shared by many modern biologists and the general public (about the status of viruses as "alive or not", see Forterre, 2016).

2.3. Lwoff's criteria to discriminate viruses from cells

The study of bacteriophages (i.e. viruses infecting bacteria) and his special taste and talent for rigorous conceptual thinking, led André Lwoff to provide the first formal definition of viruses or, more exactly, a list of properties to be used to ***discriminate*** them from cellular microorganisms (Lwoff, 1957), as follows:

1) typical microorganisms contain both DNA and RNA, viruses contain only one type;
2) all microorganisms are reproduced from the integrated sum of their constituents while viruses are produced from their nucleic acid only;
3) during the growth of a microorganism the individuality of the whole is maintained and culminates in binary fission. There is no binary fission in viruses;
4) viruses lack the system of enzymes which convert the potential energy of foodstuffs into the energy needed for biochemical syntheses (at that time called the "Lipmann system") that is present in cellular microorganisms.

Following the discovery of the ribosome, one more discriminative criterion was added (Lwoff & Tournier, 1966):

5) viruses make use of the translation machinery of their host cells.

These last two criteria (#4 and #5) make the virus an absolute parasite of its cellular host. Note that criterion #1, proposed before mRNA had been discovered, simply reflected the absence of ribosomal RNA (>80% of the cellular RNA), hence is nowadays redundant with criterion #5.

With his list of well-thought and carefully designed binary criteria, André Lwoff not only provided a rigorous and operational way to discriminate viruses from cells, while forcibly affirming his view that an infectious agent could not be intermediate between viruses and nonviruses, a possibility entertained by few microbiologists of his time, to his great irritation (page 46, Lwoff & Tournier, 1966). After fifty years of holding tight, the broadly accepted dichotomy between the viral and the cellular world appeared to be