ARTICLE IN PRESS

Studies in History and Philosophy of Biological and Biomedical Sciences xxx (2016) 1–9

Contents lists available at ScienceDirect

Studies in History and Philosophy of Biological and Biomedical Sciences

journal homepage: www.elsevier.com/locate/shpsc

Mutualistic viruses and the heteronomy of life

Thomas Pradeu

ImmunoConcept, UMR5164, CNRS, University of Bordeaux, France

A R T I C L E I N F O

Article history:
Received 23 February 2016
Accepted 27 February 2016
Available online xxx

Keywords:
Autonomy
Immune system
Microbiota
Mutualism
Symbiosis
Virus

A B S T R A C T

Though viruses have generally been characterized by their pathogenic and more generally harmful effects, many examples of mutualistic viruses exist. Here I explain how the idea of mutualistic viruses has been defended in recent virology, and I explore four important conceptual and practical consequences of this idea. I ask to what extent this research modifies the way scientists might search for new viruses, our notion of how the host immune system interacts with microbes, the development of new therapeutic approaches, and, finally, the role played by the criterion of autonomy in our understanding of living things. Overall, I suggest that the recognition of mutualistic viruses plays a major role in a wider ongoing revision of our conception of viruses.

When citing this paper, please use the full journal title *Studies in History and Philosophy of Biological and Biomedical Sciences*

1. Introduction

Viruses have generally been characterized by their detrimental effects, particularly their pathogenic ones. Examples abound of human, animal, and plant viruses that reduce host fitness, and Section 2 below recalls that, given the number of past and present human deaths due to viruses, it is by no means surprising that viruses are generally perceived as harmful.

In that context, the recent claim that many viruses can in fact be *mutualistic*, i.e., have beneficial effects on host fitness, was a bombshell to many (Roossinck, 2011; Ryan, 2009; Virgin, Wherry, & Ahmed, 2009). The aim of this paper is, via the analysis of several major examples of recently described mutualistic viruses, to assess the novelty of this claim as well as its conceptual and practical consequences. As explained below, the existence of mutualistic viruses has been known for some time, but the claim based on current data is different and much stronger that previous ones. Under its present form, the idea of mutualistic viruses raises key questions about the way scientists might search for new viruses, microbe[1]-immune system interactions, the development of new therapeutic approaches, and, finally, the role the criterion of autonomy plays in our understanding of living things. I suggest that this idea can play an important role in a more general reconceptualization of viruses, at the interface between medical and ecological-evolutionary approaches.

The structure of this paper is as follows. Section 2 explains why viruses have generally been conceived as harmful. Section 3 describes in detail several examples of mutualistic viruses. Section 4 draws four conceptual and practical consequences from the existence of mutualistic viruses. Section 5 concludes.

2. Why viruses have generally been considered as harmful

Viruses have been identified at the end of the 19th century as *infectious* agents found in a solution filtered thanks to a Chamberland-Pasteur filter (a filter that retains bacteria) (Lustig & Levine, 1992; Bos, 1999; Cann, 2012). In the footsteps of Ivanovksi, Beijerinck identified the tobacco mosaic virus as an infectious agent (a "contagious living fluid") exhibiting special features, in particular the capacity to pass through a filter that blocks bacterial agents (van Helvoort, 1996; Bos, 1999). Similarly, it is the search for small-size infectious agents that led, in the first half of the 20th century, to the discovery of many viruses (including those of yellow fever, rabies, dengue fever, poliomyelitis, measles, rubella, etc.) (Hughes, 1977). Reflecting on these very important discoveries,

E-mail address: thomas.pradeu@u-bordeaux.fr.

[1] Throughout this text, the notion of "microbe" includes all microscopic biological entities, including viruses, regardless of any decision about their living vs. non-living status.

http://dx.doi.org/10.1016/j.shpsc.2016.02.007
1369-8486/

Please cite this article in press as: Pradeu, T., Mutualistic viruses and the heteronomy of life, Studies in History and Philosophy of Biological and Biomedical Sciences (2016), http://dx.doi.org/10.1016/j.shpsc.2016.02.007

Table 1
Examples of mutualistic viruses (based in particular on (Roossinck, 2011, 2015)).

Type of mutualism	Virus	Host	Effect	References
Development	Polydnavirus	Parasitoid wasps	Indispensable for the development of the wasp eggs in the host	(Espagne et al., 2004; Bézier et al., 2009; Herniou et al., 2013)
	Endogenous retroviruses	Mammals	Made placentation possible	(Dunlap et al., 2006; Dupressoir et al., 2009)
	Murine norovirus	Mice	Can replace the beneficial effect of commensal bacteria on intestinal development and homeostasis	(Kernbauer et al., 2014)
Protection against a pathogen or disease	Pararetroviruses	Plants	Protection against pathogenic viruses	(Roossinck, 2005; Roossinck, 2008; Roossinck, 2015)
	Flaviviridae viruses	Humans	Decrease in HIV infection	(Tillmann et al., 2001)
	Herpesviruses	Mice	Protection against bacterial infections	(Barton et al., 2007)
	Lymphotrophic viruses	Mice	Protection against diabetes	(Oldstone, 1988)
	Oncolytic viruses	Mice, humans	Elimination of tumors	(Parato, Senger, Forsyth, & Bell, 2005; Miest & Cattaneo, 2014)
	Retrovirus, with ongoing endogenization	Koalas	(Probably) Immune protection	(Ryan, 2009; Tarlinton, Meers, & Young, 2006)
	Bacteriophages	*Hamiltonella defensa* within aphid host	Elimination of parasitoid wasp	(Oliver et al., 2009)
		Bacteriophage within different animal hosts (e.g., Cnidarians, fish, humans)	Protection against pathogenic bacteria	(Barr et al., 2013)
Invasion of new hosts or niches	Lysogenic bacteriophages	Bacteria	Elimination of bacterial competitors	(Bossi et al., 2003)
	Bacteriophages	Bacteria	Invasion of host	(Boyd & Brüssow, 2002)
	Fungal virus	Fungus within a plant	Thermal tolerance	(Márquez et al., 2007)

Australian virologist and immunologist Frank Macfarlane Burnet (1899–1985) writes in his influential book *Viruses and Man*: "We can define a virus then as a microorganism responsible for disease which is capable of growth only within the living cells of a susceptible host – and which is normally considerably smaller than any bacterium." (Burnet, 1955). Viewing viruses as pathogenic is consistent with the etymology of the word (from the Latin *vira*, "poison"), and with the basic assumption of the germ theory of disease (defended, in particular, by Koch and Pasteur), which asserts that diseases are due to germs (though there were tensions between the germ theory of disease and the first conceptualizations of viruses, because several scientists maintained that only bacteria could provoke diseases).

The pathogenic view of viruses has been repeatedly expressed ever since, by both the lay public and many biologists. It is particularly true, of course, of medically oriented microbiologists, many of whom define viruses as "prototypic obligate intracellular pathogens" (Nolan, Gaudieri, & Mallal, 2006; Casadevall, 1998; Kawamoto et al., 2003). Significantly, similar definitions of viruses as pathogens are found in papers by molecular biologists (Anand, Schulte, Vogel-Bachmayr, Scheffzek, & Geyer, 2008), immunologists (Jirmo, Nagel, Bohnen, Sodeik, & Behrens, 2009), plant biologists (Wu, Lee, & Wang, 2011), and virologists (Cibulka, Fraiberk, & Forstova, 2012). Adding more weight to such definitions, a number of textbooks focus on viral pathogenesis (Nathanson, 2007), and Nobel Prizes awarded to the field of virology are often explicitly presented as rewarding the discovery of disease-causing viruses, such as HIV and human papilloma virus (which causes cervical cancer, and potentially other cancers as well) in 2008 (Weiss, 2008). Overall, as observed by William C. Summers, "The basic idea that viruses are the material basis for disease transmission has changed little in the past 150 years; what has changed is our understanding of the essential properties and biological capacities of viruses" (Summers, 2014).

Of course, pathogenicity (i.e., the capacity to cause disease) is not the only way viruses can be harmful. For example, some viruses reduce host fertility (Abbate, Kada, & Lion, 2015; Sait, Gage, & Cook, 1998), or manipulate host behavior (Hoover et al., 2011). It seems more accurate, therefore, to say that viruses have generally been seen as fitness-reducing entities, most of the time through their pathogenic effects.

It is certainly not the aim of the present paper to deny that some viruses can cause significant harm. There have been dreadful viral infections in the past, including smallpox in 18th century Europe (estimated to have killed 400,000 people each year) and, following the First World War, the pandemic of influenza virus that killed over 40 million people worldwide (Loo & Gale, 2007) – many more than the war itself. Today, there are still many harmful viral infections; for example, it is estimated that by 2015, the human immunodeficiency virus (HIV) had infected more than 30 million people, with 1.8 million new infections and 1.7 million deaths in 2013 alone (Murray et al., 2014). Furthermore, many of the health alerts in the world in the last two decades were related to novel emerging viruses, including Severe Acute Respiratory Syndrome (SARS) coronavirus, and the 2009 pandemic influenza H1N1 (Chiu, 2013).

The immediate counterpart of the conception of viruses as infectious agents has been the exploration of how hosts are affected by those viruses, and the different antiviral defense mechanisms they can use. In particular, a key aspect of immunology has been devoted to understanding how hosts "fight" viruses. In textbook narratives about the historical sources of immunology, vaccination against different viral diseases is commonly the starting point (e.g., (Murphy, 2012)). This is related more generally to the interpretation of immune systems as defense systems, at war with pathogens, and especially viral pathogens (Clark, 2008). As the rest of this paper will show, however, it is inadequate to see viruses exclusively as harmful and, relatedly, to conceive of the immune system only as a defense system, selected for its capacity to eliminate microbes.

3. Mutualistic viruses

Though viruses have commonly been conceived as harmful, recent research has shown that many of them are *neutral* (not affecting host fitness) or even *mutualistic* (increasing host fitness) (Cadwell, 2015b; Roossinck, 2008, 2011, 2015; Virgin, 2014). Here I