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When viruses were not in style: Parallels in the histories of chicken sarcoma viruses and bacteriophages

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ABSTRACT

The discovery that cancer may be caused by viruses occurred in the early twentieth century, a time when the very concept of viruses as we understand it today was in a considerable state of flux. Although certain features were agreed upon, viruses, more commonly referred to as 'filterable viruses' were not considered much different from other microbes such as bacteria except for their extremely small size, which rendered them ultramicroscopic and filterable. For a long time, in fact, viruses were defined rather by what they were *not* and what they could *not* do, rather than any known properties that set them apart from other microbes. Consequently when Peyton Rous suggested in 1912 that the causative agent of a transmissible sarcoma tumor of chickens was a virus, the medical research community was reluctant to accept his assessment on the grounds that cancer was not infectious and was caused by a physiological change within the cells. This difference in the bacteriological and physiological styles of thinking appears to have been prevalent in the wider research community, for when in 1917 Felix d'Herelle suggested that a transmissible lysis in bacteria, which he called bacteriophagy, was caused by a virus, his ideas were also opposed on similar grounds. It was not until the 1950s when when André Lwoff explained the phenomenon of lysogeny through his prophage hypothesis that the viral identities of the sarcoma-inducing agent and the bacteriophages were accepted. This paper examines the trajectories of the curiously parallel histories of the cancer viruses and highlights the similarities and differences between the ways in which prevailing ideas about the nature of viruses, heredity and infection drove researchers from disparate disciplines and geographic locations to develop their ideas and achieve some consensus about the nature of cancer viruses and bacteriophages.

1. Introduction

Bacteriophages and cancer viruses may not seem to have much in common at first glance, but the two groups of viruses have shared curiously parallel histories from the time of their discoveries in the 1910s until the 1960s when André Lwoff provided the scientific community with the first modern definition of a virus (Hughes, 1977; Lwoff, 1957; Van Helvoort, 1994b). Especially notable in the histories of cancer viruses and bacteriophages is the way in which the proposals by their discoverers—that the causative agents of chicken tumors and an apparently transmissible bacterial lysis—might be viruses (D'Herelle, 1917a; Rous, 1911, 1912), were received by peers in their respective research communities. Although, the two discoveries were made by scientists working on opposite sides of the Atlantic on unrelated problems in different medical disciplines. The idea that either could be a virus was met with very skepticism in both cases (Becsei-Kilborn, 2010; Summers, 1999). In part, this resistance was due to the state of flux of the concept of virus during the early part of the twentieth century (Creager, 2002; Hughes, 1977; Van Helvoort, 1991; 1994b). Another important reason, this paper argues, was the prevalence of very different styles of research and thinking among different research groups interested in similar medical problems (Van Helvoort, 1993; 1994a). The achievement of consensus about the nature of viruses and linking of hitherto incommensurable research and thought styles led to an acceptance of the viral identity of these agents by researchers in different fields.

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Borrowing Plutarch's device of parallel biography in his *Lives*, this paper juxtaposes the histories of the discovery and reception of the Rous Sarcoma virus (RSV) and bacteriophages to show that despite differences in the specifics of disagreement, the negative reception faced by Peyon Rous and Felix d'Herelle stemmed from common intellectual roots. Interestingly, although the research communities interested in cancer research and bacterial infections did not intersect or communicate with one another at the time, many of the arguments used against the viral identities of the cancer agents and phages were remarkably similar in their lines of reasoning. In both cases there were significant differences between the research and thought styles of the discoverers and those of their opposition, which led to nearly diametrically opposed interpretations of the same data.

The discovery of the phenomenon of lysogeny in dysentery bacilli by a Belgian scientist posed a challenge, first to the idea of the bacteriophages as viruses (Bordet & Ciuca, 1921), and later more generally to the acceptance of the idea that different cellular effects could be caused by infectious agents that for generations of the host gave no other indications of their presence. Eventually it was the explanations provided in the 1950s by the French researcher Andre Lwoff about the nature of lysogeny that helped to resolve the issue and definitively identify both phages and the sarcoma agent as viruses. This paper traces the was in which lysogeny, or rather its resolution, became the lynchpin that brought about a convergence of thought styles on the nature of the causative agents of different phenomena such as tumor induction and bacterial lysis and established the criteria by which viruses are identified and demarcated from other disease agents such as bacteria today.

2. A tale of two discoveries and their reception

2.1. Peyton Rous and the chicken sarcoma agent

In 1909, a worried farmer brought to the Rockefeller Institute for Medical Research in New York City, a Plymouth Rock hen which had "projecting sharply from the right breast, a large, irregularly globular mass," (Rous, 1910, p. 697). At the time Rous, who had trained as a pathologist after obtaining his MD from Johns Hopkins Hospital in Baltimore, had just been appointed at the Rockefeller Institute by then director Simon Flexner, specifically to work on cancer research. Rous had taken up this position against the advice of his mentor W. H. Welch, who had warned him that "Whatever you do, don't commit yourself to the cancer problem" (Andrewes, 1971, p. 64). Consequently, it is not surprising that although others at the Rockefeller reportedly showed little interest in the farmer's problem, Rous seized upon the investigative opportunity as a means of vindicating his decision.

The initial examination suggested that the tumor was sarcoma, a growth of connective tissue, bits of which, when transplanted either to other parts of the host or into the breast of an unaffected fowl of the same species, induced the formation of new tumors in these locations (Rous, 1910, p. 697). Rous's conclusion from these initial studies was simply that "so far as tested, this avian tumour closely resembles the typical mammalian neoplasms that are transplantable" (Rous, 1910, p. 705). But, while earlier experimental efforts to transmit the tumors of such mammals as mice, rats and dogs using cell-free filtrates of tumor tissue had proven unsuccessful, the fowl sarcoma was transmissible by such means (Rous, 1911, p. 397). "The first tendency will be to regard the self-perpetuating agent active in this sarcoma of the fowl as a minute parasitic organism," he therefore concluded, conceding however, that:

> It is conceivable that a chemical stimulant, elaborated by the neoplastic cells, might cause the tumour in another host and bring about in consequence a further production of the same stimulant. For the moment we have not adopted either hypothesis, (Rous, 1911, p. 409).

By the following year, however, Rous felt that he had gathered enough evidence to state quite definitively that although, "experiments with the chicken sarcoma have not yielded a method whereby a causative agent can be separated from the tumours of rats and mice […] they clearly prove that the characteristics of malignant tumours in general are compatible with the presence of a living causative agent," (Rous, 1912, p. 205). Among his reasons for believing in the parasitic nature of the etiological agent was the sustained ability of the cell-free filtrates to transmit cancer even after treatments such as drying, glycerination and successive cycles of freezing and thawing, all of which killed the tumor cells themselves (Rous, 1912, p. 204). His belief was further buttressed by the finding of two other chicken tumors—a bone tumor known as an osteochondrosarcoma (Rous, Murphy, & Tytler, 1912), and a second sarcoma distinct from the first (Rous & Lange, 1913)—which were also transmissible to new birds using cell-free filtrates of the tumor. "The findings with the chicken tumours largely demolish the theoretical basis on which objections to an extrinsic cause for cancer have been built up," Rous concluded upon finding the osteochondrosarcoma, (1912, p. 1794), following up with an even stronger claim a couple of years later, that "It is perhaps not too much to say that their recognition [of the agents of these tumors] points to the existence of a new group of entities which cause in chickens neoplasms of diverse character" (Rous & Murphy, 1914, p. 68).

In what is now an near-canonical account of the history of cancer and viruses, Rous' claims and conclusions about the possible extrinsic, infective nature of the cancer agent were either rejected outright or met with considerable skepticism from the leading cancer-experts of the day (Andrewes, 1971; Becsei-Kilborn, 2003, 2010; Dulbecco, 1976; Van Epps, 2005). Rous's discoveries came during a time of a growing consensus in the cancer research community that cancer was not an infectious disease and that its origins lay somewhere in the cell's own inner mechanisms (Becsei-Kilborn, 2003, p. 2). His case was doubtless also hindered by the fact that he was unable to isolate any observable organism from any of these tumors, the morphologies of which also showed no evidence of infection, at least in any conventional sense. While he appears to have held fast to his notion of a viral cause for chicken sarcoma, Rous could not find similarly transmissible sarcoma or other tumors in any of the mammalian models. Consequently he turned his attention to other medical problems such as blood biochemistry, which perhaps seemed more urgent at the time (Becsei-Kilborn, p. 112). Although he eventually returned to the cancer problem, this later work focused on the Shopes papilloma virus, and Rous never worked with the sarcoma agent again after 1915. Studies on the chicken sarcoma, however, did not languish for long either at his home institution or abroad, a point I shall return to later in this essay.

2.2. Felix d'Herelle and the phenomenon of bacteriophagy

At its outset, the story of Felix d'Herelle's discovery of the bacteriophage bears little resemblance to Rous' experience with the sarcoma agent. Whereas Rous, despite his maverick ideas, was very much part of the mainstream research establishment—having trained at one of the most renowned medical schools in the United States – d'Herelle (1873–1949) was an outsider to the medical research community. Of French-Canadian or *Quebecois* origin, d'Herelle was never formally educated beyond high-school. He gained his knowledge of microbiology largely through self-instruction, obtaining practical experience in a private laboratory he set up in his home in Montreal in 1897 (Summers, 1999, p. 5). He later gained recognition within scientific circles by working on a number of diverse problems for various scientific commissions in