ANDREWES’S CHRISTMAS FAIRY TALE: ATYPICAL THINKING ABOUT CANCER AETIOLOGY IN 1935

by

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This paper uses a short ‘Christmas fairy-story for oncologists’ sent by Christopher Andrewes with a 1935 letter to Peyton Rous as the centrepiece of a reflection on the state of knowledge and speculation about the viral aetiology of cancer in the 1930s. Although explicitly not intended for public circulation at the time, the fairy-story merits publication for its significance in the history of ideas about viruses, which are taken for granted today. Andrewes and Rous were prominent members of the international medical research community and yet faced strong resistance to their theory that viruses could cause such tumours as chicken sarcomas and rabbit papillomas. By looking at exchanges between these men among themselves and other proponents of their theories and with their oncologist detractors, we highlight an episode in the behind-the-scenes workings of medical science and show how informal correspondence helped keep alive a vital but then heterodox idea about the role of viruses in causing cancer.

Keywords: cancer aetiology; tumour viruses; informal scientific correspondence; Christopher H. Andrewes; Peyton Rous; oncologists

INTRODUCTION

‘I greatly look forward to [your] Harvey lecture. If you let yourself go on that, I can let myself go too’, wrote the British virologist Christopher H. Andrewes (1896–1988) to his friend, the American medical researcher Francis Peyton Rous (1879–1970) on 6 December 1935, regarding his speculations on the mechanisms by which viruses might be able to cause cancer.1 The particular way in which Andrewes ‘let go’ was by bringing elements of metaphor, analogy, satire, sarcasm and popular science-writing to articulate a complex and contested scientific hypothesis in the form of a fairy tale. As he confided to Rous: ‘The ideas are rather woolly for public demonstration, but as it will be nearly Christmas when this letter arrives, I present them as a Christmas story for oncologists. (Let Shope see it).’2

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The letter and fairy story, written on the same day as Rous delivered his lecture, are a part of a decades-long correspondence between Andrewes, Rous and the British cancer researcher William E. Gye (1884–1952), sharing their thoughts about the viral aetiology of cancer. However, although freely available for viewing at the American Philosophical Society’s library, this particular fairy story has remained unpublished until now and, save for one very recent citation, unremarked upon to this day. We believe that it merits publication as much for its content as for its style. Barely a page of typescript in length, it nevertheless packs in some serious scientific punches couched in whimsy of the type that would have done Hans Christian Andersen proud. ‘[W]hatever the truth it has the ease proper to good literature. Like “The head soldier” it ought to be true and like “The Little Match Girl”’, wrote Rous appreciatively after seeing it.

In this paper we present a close reading and historical analysis of the story, contextualizing it against the correspondence of which it was a part and against the intellectual environment of those times. When this story was written, Andrewes, Gye and Rous, although well respected in the medical research establishment (for example, all would soon become members of the Royal Society), held opinions about tumour causation that went very much ‘against the grain’. The received knowledge among mainstream oncologists—mostly clinicians or pathologists with clinical experience of patients, who were primarily interested in cancer treatment and management—was that cancer in humans was not contagious. But laboratory researchers such as Rous, Andrewes and Gye consistently turned up experimental evidence that pointed to the involvement of viruses, known agents of infectious disease. In the face of stiff opposition from the establishment, it was through their correspondence that they were able to shape, test and build on their ideas and keep theories of a viral aetiology for cancer alive. By looking at the exchanges between them, this paper illuminates an episode in the behind-the-scenes workings of medical research, showing how informal exchanges and brainstorming among scientists played a vital role in the formulation of what was simultaneously a Kuhnian revolution and a resurrection of a denounced topic in cancer research: the notion that tumours could be caused by ‘living’ entities.

In addition to revealing a hidden chapter in the history of ideas about viruses and their much-debated role in cancer aetiology, this story also has a broader significance for the historiography of virology. There has been a tendency in most histories of virology of this period to emphasize the role of bacteriophage (bacterial virus) studies and molecular genetics in the elucidation of the behaviour of viruses. In such accounts the major advances in animal virology have often been relegated to the isolation of such tumour-causing agents as the Rous sarcoma virus and Shope’s rabbit papilloma virus. By highlighting certain early, under-acknowledged contributions on the nature of host–virus relationships, we show how many fundamental questions about this issue had already been formulated by the mid 1930s. There was an active transmission of ideas between the bacteriophage scientists and animal virologists, and Andrewes occupied a prominent place at the crossroads. So, before diving into the text and offering our interpretations we provide some background to the correspondents as well as the state of knowledge and speculation over viruses and cancer at that time.

The ‘Three Musketeers’ of Tumour Viruses

Once, fairly early in the course of their correspondence, Rous referred to himself, Andrewes and Gye as ‘the Three Musketeers,’ a reflection of how he perceived their roles—as
guardians of the bastion of tumour viruses against its many opponents. Of the three he was the one with the longest association with the topic, having discovered the existence of a filterable cause for a tumour while investigating a case of a sarcoma—connective tissue tumour—in a chicken that a worried farmer had brought his way in 1911. His preliminary analysis showed that the tumour was transmissible, either by transplanting bits of sarcoma tissue or by injecting cell-free filtrates thereof, into unaffected birds of the same species. Further investigations led him to conclude that the sarcoma was caused and propagated by ‘a minute parasitic organism’.

Rous’s proposal appeared hard on the heels of an international conference of leading cancer physicians and researchers from the UK, the USA and Europe, where the attendees had arrived at a consensus on the matter of cancer aetiology that ‘cancerous tissue is really a biological alteration of the tissue proper to the individual attacked by the disease, and that its peculiar properties may be explained without assuming the intervention of extraneous agencies, such as a hypothetical cancer virus.’

As discussed in earlier publications, this consensus had been born of a long debate, dating back to the inception of the germ theory of disease in the nineteenth century, between two schools of thought on the endogenous (that is, cellular) versus exogenous (parasitic) origins of cancer. In addition to the lack of evidence, namely the failure to isolate any cancer parasite, practising oncologists were also resistant to any explanations for cancer that implied that it might be an infectious (or contagious) disease. According to their line of argument, had cancer been a contagious disease, ‘doctors, nurses, surgeons, pathologists, who come into daily contact with cancerous tissue without taking any special precautions, ought to be particularly liable to it. But they are not.’ Consequently it was difficult to accept the idea of viruses as a possible cause of tumours. So firmly did they maintain this belief that cancer researchers and physicians passed a formal resolution at an international conference in 1927 saying that ‘it may be accepted for all practical purposes that cancer is not to be looked upon as contagious or infectious.’ This message was also emphasized in public education films about cancer produced by the American Society for the Control of Cancer (renamed the American Cancer Society in 1944), as discussed by the historian David Cantor.

Given such beliefs, it is not surprising that Rous received little support for his conclusions about the possible role for viruses in causing tumours, even after he found cases of other new transmissible bird tumours. The implications of his findings were confounded by the fact that the tumours he found were in birds, which clinicians did not find relevant to cancers in humans or other mammals, especially in treatment or management, which were their primary concerns. Owing partly to this negative reception and, more importantly, to the lack of any headway, either in isolating observable organisms from the different bird tumours or in finding mammalian tumours capable of transmission via cell-free filtrates of their tissues, Rous abandoned active research on the sarcoma viruses for good. As he later explained to Andrewes, ‘I’d become pinched and parched mentally as [a] result of continually negative experimentation, and felt that only new outlooks could cure.’ But he remained deeply interested in the cancer virus problem and eventually (after a hiatus of 20 years) resumed active research on the subject for a further 30 years. Looking back over his career many years later, he said:

When I quit the tumor problem in 1915, only two of its aspects had any drawing power for me: a) the make-up and nature of the chicken tumor virus, an undertaking for which I had neither the knowledge nor technique; . . . b) the virus causation of tumors in general.
To this I would have gladly returned at any time if opportunity arose. It didn’t arise, but was given by that great fellow Dick [Shope], who knew of my long hankerings. Immediately after reporting upon his newly discovered papilloma virus, … he offered [it] to me to do with as I wished, fancy free.22

The Shope rabbit papilloma agent proved to be a useful experimental model for Rous in many ways. The fact that it was a mammalian tumour virus addressed one of the main objections that oncologists had against considering the viruses as tumour agent: avian tumours had no bearing on cancers in humans or other mammals. For instance, according to cancer pathologist James Ewing (1866–1943) of Cornell Medical College and Memorial Hospital in New York, ‘this disease is clearly sui generis, and observations upon it may not be transferred safely to any other’.23 The rabbit papillomas also enabled Rous to approach his problem-solving from a completely different route than before. Whereas earlier he had been unable to isolate any filterable agents from recognized mammalian tumours, he now had a proven virus isolated from rabbit warts, which showed the ability to transform warts into malignant tumours. Armed with such new tools, he proceeded to expand on his ideas on the development of cancer, ‘ideas which are now part of our basic knowledge of the disease’.24

Meanwhile, however, Rous had not destroyed any of the chicken sarcoma material and for many years his laboratory continued to supply dried material to anyone who requested it. Among these myriads of such recipients of this material was Gye, the person widely credited with bringing the Rous sarcoma virus back into the spotlight as a candidate for cancer causation.25 Trained in chemistry before he went on to study medicine, Gye had become ‘thoroughly steeped in the cancer problem’ at the Imperial Cancer Fund in London, where he was a member of the staff from 1913 to 1914.26 He joined the Medical Research Council in 1919 and started to work on the Rous sarcoma agent some time around 1923. ‘He came to it expecting to find it chemical in character, not a virus; but he was soon convinced otherwise’, particularly because he was able to confirm most of Rous’s results pointing to the same conclusions.27 He seems to have contacted Rous for the first time to inquire about casual reports he had heard on success with sarcoma virus cultivation at the Rockefeller Institute in New York. ‘My own work, which began last spring time, has been up to a point surprisingly successful’, he wrote, adding, ‘I am now able to cultivate an organism regularly from tumour filtrates.’28

Although nearly a decade removed from the field by then, Rous’s response shows him immediately appreciative of and responsive to Gye’s missive:

Everything you tell about the cultivation of the agent causing the chicken sarcoma has an intense interest for me who strove nearly two years at that job, years rendered the more unprofitable through my inborn lack of aptitude for bacteriology. People talked then as now of a ‘chemical’ agent causing the sarcoma and, presumably, other causes. … I am rejoiced that you have already got this far.29

Gye’s idea, namely that there were two separate factors in tumour formation—one an extrinsic, filter-passing, infective agent (the virus), and the second an unstable cell-specific chemical factor—came in for a flood of criticism from different channels. Nevertheless, he was a visible figure in the cancer research community, including as director of the Imperial Cancer Research Fund from 1935 to 1949. As Andrewes noted in Gye’s obituary notice: ‘His influence on thought concerning tumours was, and continues to be, immense. The virus theory of tumours had been practically written off until he
re-awakened interest in it.' Although Rous admitted privately to Andrewes that ‘Between ourselves [Gye’s] work on the specific factor got me into a jam when visiting England in 1926–27, so many people ... expected me to endorse it’, he added: ‘Will himself never even hinted that I should do so, then or later. His was always a chivalrous attitude. He seemed to regard me as an innocent whom it would be unfair to drag into the hurly-burly of this world.’

Other correspondence between Rous and Gye reveals that, at least in the early years, the traffic of ideas and advice flowed both ways. Before a meeting, for example, it was Gye to whom Rous would turn:

> Please look at the Harvey Lecture table comparing the attributes of the tumor agents and the viruses, and let me know whether you think it should be shown. A table barks at one whereas sentences often merely murmur. But perhaps there are reasons why this particular table will be inadmissible.

Gye’s response entertained none of Rous’s doubts: ‘Visual impressions are so much keener than aural impressions that I’m sure a mere sight of the table would teach more than 20 mins of talking. I know of no reason why the table should not be shown.’

On another occasion, upon receiving certain reprints, Gye commented: ‘You are very very cautious—may I say timid?—in your discussions and conclusions’, admitting, however, that ‘it’s well we are not all reckless’. To Rous personally, then, irrespective of their theoretical disagreements, Gye was ‘a fountain of generosities, richer than those founts that ran wine in the Middle ages’.

The youngest member of the trio, Andrewes, was also the only one who had a genuine claim to expertise on viruses. But he more than made up for potential gaps in knowledge of the others, ‘not merely because of his own ability but because of his experience and association with the strong British group of workers in the virus field’. Andrewes was introduced to viruses while a medical student, conducting his first laboratory investigations under the guidance of Mervyn Gordon at St Bartholomew’s Hospital Medical School in London. He trained in pathology after obtaining his basic medical degree, during which he worked in the USA with the Rheumatic Fever Service at the Rockefeller Institute from 1923 to 1925. It was during this time that he met Rous, with whom he would maintain a lifelong friendship and correspondence.

On his return to England, he was initiated into the cancer virus problem by Gye, whose scholarship had so impressed Andrewes’s father, Sir Frederick Andrewes, also a physician, that he requested that his son work with Gye on the cancer problem. The two men worked together for a couple of years, specifically investigating the filterability of the Rous sarcoma agent from different sources. In 1927 the younger Andrewes joined the staff of the National Institute of Medical Research (NIMR) in Hampstead Heath, London, and began a period of research that he would later describe as ‘an exciting period in the early days of virology with discoveries coming in thick and fast’. He soon established himself as an expert on animal viruses and, later, bacterial viruses as well, publishing numerous papers on different aspects of his research. Although they were not his primary focus, Andrewes maintained an active interest in tumour viruses through immunological and physical (for example centrifugation) studies as well as through his exchanges with Rous. Meanwhile, even after their collaboration ended and he moved to the NIMR, he remained in cordial contact with Gye.
The importance of their correspondence in keeping the ‘Three Musketeers’ in the thick of wider discussions and debates about cancer is evident from their prominence beyond their immediate intellectual circles, even in such times when their work was not directly concerned with the subject, and their beliefs regarding cancer viruses were far from popular. After he became the director of the Imperial Cancer Research Fund in 1935, Gye repeatedly directed attention to Rous’s discovery, which he deemed ‘of cardinal importance’, emphasizing its implications for understanding cancer causation more broadly:

unlike the chemical substances, radiations or gross parasites which can start a tumour and, once the tumour has started, are no longer necessary for the continued growth and multiplication of the malignant cells, the virus particles multiply and are obtainable again and again in large quantity and retain the power to start a tumour afresh. They have a different function in cancer; they are the continuing cause of the tumours in which they can be demonstrated.

Although Andrewes and Rous were not in such influential positions, the reputations they gained in their respective spheres—the former as a virologist and latter as a pathologist and, since 1924, as the editor of The Journal of Experimental Medicine—also gave them opportunities to disseminate their ideas to a wide public. For example, when invited to deliver the Oliver–Sharpey lectures for the Royal College of Physicians of London in 1934, Andrewes chose to focus on the subject of the virus theories of cancer causation. Even as he acknowledged that the subject of tumour aetiology was ‘rather far removed’ from those dealt with by previous lecturers, he stressed the fact that the ‘parasitic theory of cancer needs to be carefully reconsidered in the light of our growing knowledge about viruses’. His lectures proved controversial because the findings of both Gye and Rous featured prominently, but at no cost to his growing status in virology. The following year, Rous also chose the same subject as the focus of his Harvey lecture, which, as will be discussed later, further stirred things up.

In the absence of any positive results or encouragement from most other researchers, then, one can see how it was through testing various ideas against each other via this correspondence that these three men kept themselves current about viruses and able to guard the fledgling theory against various challenges from its detractors. ‘If you’ve any criticisms, be outspoken about them, won’t you? We are the Three Musketeers, you know, and must carry something more than blunderbusses’, wrote Rous to Gye, employing language of weaponry to emphasize the inadequacies of the older armoury of arguments (the short-range blunderbusses) and the need to use the newer generation of muskets—precisely targeted arguments based on data and experiments—to make sure that their protégé did not die a premature death. Only in the privacy of these exchanges did these men dare to express their personal reservations and discouragement. Even Andrewes, ever the public champion of the virus theory, would confess once to Rous: ‘I crave your help for the cancer problem puzzles me (I am beginning to wonder whether viruses have anything to do with it).’ It is obvious, then, that all three relied greatly on one another for ideas and evidence, not just affirmation or moral support. The fairy story, discussed in detail in the next section, is a fine entry point into the private, behind-the-scenes conversations and speculations that took place between these men. It is unique in form and genre as the only piece of fantastical writing in the entire correspondence; neither Rous nor Gye seem ever to have diverted their energies in this manner, although we know that Andrewes used humorous fiction as commentary on at least one other occasion,
many years later, on a completely different topic.\textsuperscript{50} But the intellectual content of the fairy story is very much representative of the common thread that runs through the entire correspondence between himself and Rous.

\textbf{READING THE LINES AND BETWEEN THEM}

Written in the early part of the twentieth century, Andrewes’s piece might be viewed as a product of the mutual give and take between literature and science that had become popular in Britain during the nineteenth century.\textsuperscript{51} His fairy story undeniably conforms to Melanie Keene’s description of the stories produced in the nineteenth century as ‘an important new way in which nineteenth-century Britons enthused about, communicated, and criticized the sciences’.\textsuperscript{52} Just as Andrewes did in his story, the different inhabitants of the worlds of fantasy were used in different ways in these stories: ‘as framing devices, as storytellers, as starring characters, as illustrations, as the invisible forces of nature’.\textsuperscript{53} But there are important points of departure from the examples cited by Keene. For one, her commentary refers to works that were actually published, such as Charles Kingsley’s famous \textit{The Water Babies}; although Andrewes may have intended his story to be shared with limited audiences, it was never published. Additionally we know he wrote his short fairy story for his peers, unlike the Victorian works, which were primarily chosen for their utility in ‘presenting scientific and technological knowledge to young audiences.’\textsuperscript{54} The fairy tale also bears no similarities to the type of writing represented by the hitherto unpublished geological poem \textit{The Professor’s Descent}, which the literary scholar Ralph O’Connor has attributed to the geologist, clergyman and Oxford don William Buckland (1784–1856).\textsuperscript{55} Like Andrewes’s fairy story, this poem was directed at an audience of peers, not youngsters; however, whereas O’Connor has convincingly shown that \textit{The Professor’s Descent} was ‘a geological parody of Thomas Gray’s Norse ode \textit{The Descent of Odin}, to claim a similar parallel for Andrewes’s tale would be a stretch. True, he labelled it as a Hans Christian Andersen version rather than one by the Brothers Grimm (see Appendix 1), but nowhere in the story or elsewhere did he identify any single one of the more than 100 fairy tales that Andersen had published in his lifetime as a model for his own.\textsuperscript{56} His labelling of his offering as a ‘fairy story’ then seems to have been for the exact reasons he gave Rous: namely, that it was then close to Christmas, a time of year traditionally associated with the telling (or reading aloud) of fairy tales. As for Hans Christian Andersen, it is easy to imagine that the similarities in the names—and especially the anagram between their initials, HCA and CHA (his favoured signature in letters)—could have influenced his choice.

Andrewes’s story opens with the familiar ‘Once upon a time’, in the time-honoured tradition of all good fairy tales, and also contains a few other familiar tropes, such as the use of ‘Now’ to segue from one part of the story to another, and references to feudal systems reminiscent of the settings of such tales—all of which lend the work an aura of the fairytale genre. But instead of being populated with beautiful damsels, wicked witches, Prince Charmings and such, it immediately switches gears and brings the reader’s attention to a ‘family of viruses’:

\begin{quote}
Once upon a time there was a family of viruses, much like other viruses. Some of them liked mutton, others poultry. Some of them multiplied wantonly in the cells they
\end{quote}
inhabited, and smashed up their homes; others, more restrained, practiced a magic which caused their homes to proliferate.\(^{57}\)

For the most part this introductory paragraph is simply a packaging of the then known facts about viruses, which could be found in the writings of such prominent virologists as Thomas Rivers (1888–1962), another of Rous’s colleagues at the Rockefeller Institute with whom Andrewes maintained a long friendship.\(^{58}\) Information such as the specific affinities that different viruses had for different hosts and about the types of cellular damage, for example necrosis, that they inflicted, are presented here playfully in the guise of the cellular ‘homes’ being ‘smashed’. But immediately thereafter, Andrewes throws down his first gauntlet, suggesting that instead of destroying their host cells—the viral ‘homes’ in the passage above—viruses could induce tumour formation specifically by instigating them to ‘proliferate’. Then as now, the unchecked proliferation of cells was considered a trademark feature of cancer and thus did not need to be explained, certainly not to an audience of oncologists. Indeed, despite the ‘for oncologists’ in its title, cancer or tumours are not mentioned in the fairy story until nearly the end, but the omission is not all that surprising considering the purported audience. After all, oncologists were experts on cancer and knew these salient facts. It was the potential—in his view, realized—role of the viruses in the cancer process that Andrewes wished to emphasize, bringing to the attention of oncologists the possibility that they could as easily cause cellular proliferation as they could necrosis.

One point that bears some discussion here is what exactly Andrewes meant by the term virus. As the historian Ilana Löwy argued in her analysis of the difficulties of relying on scientists’ own accounts of their past activities, many scientific terms do not ‘possess a single, well-defined meaning’. Moreover, ‘scientists themselves may not perceive the changes in meaning of the very terms they use’, even within the bounds of their disciplinary expertise.\(^{59}\) The term virus is a particularly good example, with its meaning in a state of flux at least until the 1950s: at the end of the nineteenth century it was used to mean any agent of infectious disease, whereas by the 1930s it was used only for those in the filterable category.\(^{60}\) When Rous began his investigations, his conception of the sarcoma agent fitted somewhere between these two extremes: he viewed it as an extremely tiny living organism that was ‘ultramicroscopic’\(^{61}\)—invisible under a light microscope—and could pass through bacteriological filters impermeable to the smallest known bacterial species.\(^{62}\) It is interesting to note, however, that apart from a single report on the nature of the unknown causative agents of the different bird tumours, Rous refrained from using the term virus in his early publications.\(^{63}\) ‘I wanted to call the tumor cause a virus’, he later told Andrewes,

but the crusty, redoubtable, lovable old Secretary of the Board of Scientific Directors, Dr. [T. Mitchell] Prudden, whose wisdom I admired, put his granite foot down against it, suggesting ‘agent’ instead; and though I called the thing a virus when lecturing, and Gye had no doubts in the matter, many workers in this country held to [James B.] Murphy’s view according to which all was left agreeably mysterious.\(^{54}\)

Elsewhere he also confessed that Prudden had done him ‘a good turn, since the virus proved in some ways so peculiar that not until the time of my Harvey lecture in 1934, when the traits of viruses generally were better realised could it safely be called as such.’\(^{65}\)
Rous's initial description of the sarcoma virus was certainly flexible enough to be accommodated within the parameters of the definition of viruses in the 1930s as infectious agents of extremely tiny size—accounting for both their ultramicroscopic and filterable characteristics—with the additional property of obligate parasitism, 'in the sense that their reproduction is dependent on living cells.' The inclusion of obligate parasitism in the list of basic properties explained the seeming failure to culture viruses in medium once separated from the source of infection. Viruses were cultivable, but because they were obligate parasites their growth could be observed only in living cells, not in vitro.

Not working directly with infectious diseases, clinical cancer workers considered such issues of identity irrelevant; for them the main thing was that viruses were infectious. And because in their view cancer was not infectious, it followed that viruses could not be involved in cancer causation. For Andrewes, however, such a problem did not exist. Although he agreed, even stressed, that tumours were not infectious, he argued that an infection—with any sort of living pathogen—need not necessarily be equated with infectiousness or contagiousness, citing examples of bacterial infections to make his point:

If tetanus were due to a virus and not to a cultivable bacterium, there would be but little more evidence of its parasitic origin than is available for cancer. Again, most cases of malignant endocarditis are caused by infection of the heart valves with an ordinarily harmless saprophytic streptococcus; no connexion can be traced between one case of the disease and another. . . . Clearly then, a disease of parasitic origin need not be demonstrably infectious, and this objection to the virus theory of cancer cannot be stressed unduly.

In other words, the outcome of host–parasite interactions was as dependent on the environment or milieu surrounding the agent as the presence of the microbial agent itself. Depending on the particular conditions, the same bacterium could be saprophytic or pathological. Such a conception of viruses was well in keeping with those of other leading virologists of the time, who stressed a definition 'emphasising the intimate relation that exists between them and their host cells'. The following excerpt of a letter from Andrewes to Murphy, Rous's former and earliest colleague on the sarcoma work, exemplifies how the nature of this relationship had become the crux of the debate between oncologists and virologists:

Now the hosts didn't like this business and they defended themselves. . . . Or else they made terms with the enemy and said 'Come right in and live in our cells. But you must practice birth-control and leave the furniture alone. If you do that you may come even into the inner sanctum of our germ plasm and be tolerated as feudal retainers from generation to generation.'

Despite the seemingly innocuous beginning with its perfectly reasonable claims about the way in which the cells of a host organism could defend itself against viral parasites, this second paragraph makes some very controversial and startling claims. The first, where the
host cells invite the viruses to ‘come right in and live in our cells’, is an extension of an idea
Andrewes had already essayed, privately and in more detail to Rous: ‘I keep brooding along the lines that the cancer virus is a normal symbiont of the cells of all of us and only declares itself when the controlling mechanism gets out of gear’, he had written, adding optimistically, ‘I know you incline to think on the same lines.’ Rous’s response, that the idea of symbiosis was ‘more daring than I have dared’, did not provide as much affirmation as Andrewes would perhaps have liked. Although he had a clear enough rationale for his idea that ‘in its disease-producing state I cannot conceive of it as other than an intracellular parasite; I therefore find it hard to believe that in its harmless (? saprophytic) condition it should be extracellular,’ Andrewes acknowledged the fact that he had no evidence to back up his reasoning, which furthermore ‘isn’t necessarily sound.’ In his Oliver–Sharpey lecture he toned down and merely offered the suggestion that ‘a symbiotic virus might occur in normal cells’. But in his story he gave freer rein to his imagination with the proposal—clearly at odds with the conventional view and more radical than his own idea of symbiosis—that the host laid out ‘conditions’ or terms whereby the viruses were to curtail activities such as their reproduction, namely ‘practice birth-control’, while inhabiting the cell.

A second idea, quite revolutionary in the 1930s, especially in the context of interactions between viruses with their human or other mammalian hosts, was the proposal that the site of this intracellular parasitism might be the host cell’s germ plasm. The suggestion was not completely new; rather it resembled the model put forth just a few years earlier by the Australian virologist Frank Macfarlane Burnet to explain the phenomenon of bacteriophage lysogeny. In attempting to choose between certain diametrically opposed views on the nature of the bacteriophage, Burnet had examined the phenomena of both classical bacteriophagy (the transmissible lysis of certain bacterial species) and lysogeny, the seemingly spontaneous production of bacteriophage particles from bacteria that could exist for generations without showing signs of their presence (that is, through lysis). On the basis of the results of his careful investigations, he concluded that the two sides were not in as much conflict as imagined. With specific reference to the problems posed by lysogeny, Burnet explained: ‘The permanence of the lysogenic character makes it necessary to assume the presence of bacteriophage or its anlage in every cell of the culture, i.e., it is part of the hereditary constitution of the strain.’ Substitute the words ‘germ plasm’ for ‘hereditary constitution’ in the passage and the explanation—as a genetic symbiosis—virtually echoes, or rather is echoed by, Andrewes’s account of the feudal relationship between the viruses of mutton or poultry with their host cells!

That Andrewes was familiar with Burnet’s work is not surprising. The two men had collaborated on the physicochemical characterization of bacteriophages and had even published a paper together on the nature of viruses. What is puzzling is the fact that despite this shared history, Andrewes had, until this Christmas story, explicitly avoided discussing the notion of viruses in a genetic symbiosis with their hosts on the grounds that there was too little information about the nature of the genes:

It is difficult to argue positively about the possible behaviour of a biological agent which has never yet been shown to exist in a free state. Nor can one readily deny that a tumour agent may have similar physical properties to a gene, when the latter are purely a matter for conjecture. . . In our present state of knowledge it seems wiser on the whole to confine our speculations to less fantastic channels.
Andrewes did not cite Burnet’s work on the subject of lysogeny in his Oliver–Sharpey lecture, but by the following year he was freely incorporating Burnet’s model for bacteriophage lysogeny into his fairy story about cancer viruses. Some years later he also drew on the example of lysogeny to make a case for the role of latent viruses in cancer in his presidential address to the Royal Society of Medicine—emphatically not a ‘fantastical channel.’ Precisely what caused his about-turn is hard to discern from the accessible archival and published material. Certainly there does not seem to have been anything new by way of either evidence or argument added to the scientific picture in the interval between Andrewes’s lecture and the fairy story. A footnote at this juncture suggests that Andrewes was aware not only of the scepticism with which cancer researchers viewed the idea that viruses could be normal symbionts but also that he himself still harboured some doubts about the proposed mechanism: ‘This is Hans Andersen’s version. Grimm says they were only allowed to live a saprophytic existence in the Servant’s Hall and weren’t allowed in the cells at all. I don’t know which is right. C.H.A.’

Such misgivings notwithstanding, the next paragraph shows Andrewes adopting ideas about virus latency similar to those in lysogeny quite thoroughly into the tumour necrosis factor virus: ‘In this feudal existence most of the viruses lost all ambition and ceased to clean their teeth, which became subject to dental caries and fell out. And after a few generations the race was quite tuskless.’

The metaphor of viral tusks and tusklessness that Andrewes introduced here proved quite far-reaching, because it provided several new ways for considering the nature of tumour viruses and their relationship with their host cells. One of the biggest challenges to the viral aetiology of cancer had been the fact that no virus had ever been isolated from mammalian tumour tissue. Andrewes’s metaphor suggested a possible explanation for the fact. Because most viruses were invisible with the available visualization techniques of that time, the standard method to ‘observe’ them was through indirect means, for example serological evidence and the pathological effects on host cells. If the viruses were somehow rendered ‘tuskless’—in the fairy story, by mutation—it would not be possible to determine their presence in an extract of host cells. As Andrewes told Rous:

> If there is a grain or two of truth amongst my chaff, it is reasonable to believe that the virus-induced tumours which form the bulk or the whole of mammalian neoplasms may never be filterable—unless by chance one finds a way to favour an odd mutant with tusks.

Andrewes later used the same metaphor to expand on this idea in his presidential address:

> Such findings make one wonder whether a virus may not depend for its power to infect normal cells on some . . . aggressive mechanism, teeth as it were permitting an entry into the new cell; and whether in certain circumstances a virus may not lose its teeth by disuse-atrophy, as armadillos and ant-eaters have done. This could happen most readily, one may imagine, in the environment of the cancer-cell, where virus could be carried on from cell to daughter and granddaughter cell as cell-division was stimulated and the need to come out of the cell to look for fresh prey would disappear. Viruses which had become toothless by some such process could thus act as a proximate cause for cancer and yet one would never be able to demonstrate their presence by injecting tumour-extracts.
Now, as a result of his experience with various types of infectious material—‘Rickettsia-like organisms occur in normal inert cells, symptomless viruses in normal potatoes, latent phages in normal bacteria and even harmless streptococci in normal throats’—Andrewes had no problem in believing that non-pathogenic cancer viruses could exist in precancerous cells. But the conservative cancer pathologists, for whom viruses were a group of filterable agents whose presence during infections was so characteristic as to be of diagnostic value, could not or would not consider such possibilities, leading to Andrewes’s disgruntled observation: ‘And pathologists, who thought that all viruses had tusks, studied the neoplasms and grunted into their beards “The parasitic hypothesis of cancer is dead.”’

In the final, very brief, paragraph the fairy story turned to the impact of evolution on the outcome of the host–virus relationship. This subject was another ‘fantastic’ realm, because viruses and evolution were not normally spoken of together at that time. Even Rivers, the acknowledged expert on viruses, had not mentioned evolution in his authoritative reviews on viruses published in 1927 and 1932. Only in the 1940s would Burnet publish his landmark Virus as organism, which dealt specifically with evolutionary aspects of viruses involved in human disease. Andrewes’s own and considerable contributions to the subject of viruses and evolution came even later. But even in the few sentences in the fairy story we see the glimmerings of some deep thinking about the role of evolution in the eventual manifestations of host–virus interactions. In his scenario, viruses mutated to their toothless state and the host cells armed themselves against attack by cancer viruses. Once such an equilibrium had been reached, the virus infection would no longer impede the reproduction of the host organism. Because the propagation of the species, rather than the survival of an individual organism of that species, was the foremost evolutionary goal, the ‘goddess’ evolution would not interfere in the development of cancer when a virus grew new tusks. As Andrewes pithily concluded his story, when the hosts, panicked at the incidence of cancer, prayed to her for help: ‘alas, the goddess had no interest in diseases which attack creatures after they have successfully propagated themselves, and turned a deaf ear to their prayers.’

WORTHY FOES: THE EPONYMOUS ONCOLOGISTS

Who were the oncologists in the title of the fairy story? Before addressing that question, it may be worthwhile to consider exactly what Andrewes meant when he used the term ‘oncology’. A 1915 text identifies the ‘science of oncology, which comprehends tumors of all kinds, whether malignant or benign or ill defined’. The term oncologist by extension would therefore have signified a clinician who dealt with the gamut of problems relating to cancer. While he did not name any specific oncologists either in the story or in his letter to Rous, Andrewes’s language is too pointed to believe that he did not have at least one imaginary adversary in mind when he marshalled his facts and crafted them into this tale. Certainly it would permit a better contextualization of the content and tone of the story if one knew something about the adversaries whose ideas he could articulate arguments against. There are many possible candidates for the role of the eponymous oncologists, because as indicated by the outcomes of the two international cancer congresses discussed above, the community as a whole did not want to revive the parasitic theory of cancer. However, on the basis of clues from the letters written back
and forth and in their publications, we suggest Murphy and Ewing—both New York-based physician-scientists of considerable stature and staunch opponents of viral theories of cancer causation—as the most likely candidates for the oncologists’ role.

Murphy is the more obvious choice, because his association with the sarcoma agent went back to 1912 and in fact lasted much longer than Rous’s own.\(^89\) Although he neither disputed characterizations of the sarcoma agent in their joint papers nor engaged in any known debates with Rous on the subject, Murphy would reveal a few years after they had parted ways that he had ‘never believed in the virus theory’.\(^90\) Andrewes and Murphy maintained a correspondence with one another independently of their association with Rous, but their relationship does not seem to have reached the level of easy camaraderie that existed between Andrewes and Rous.\(^91\) One major reason may have been their intellectual differences—the matter of the viral cause of tumours would ever be a bone of contention—but their letters to each other were not devoid of banter: ‘Hoping you’ve made a New Year’s resolution to refer to the tumour agents henceforward as viruses’,\(^92\) wrote Andrewes to Murphy, to which the latter replied:

I am shocked by your suggestion of a New Year’s resolution. Don’t you realize that I am essentially a very kind person and wouldn’t think of doing anything to deprive other people of pleasure? You must know with what zest Tom Rivers includes the chicken tumors among virus diseases, because he thinks he annoys me, and I rather suspect one or two others of getting some satisfaction in criticizing my point of view. . . So now I am afraid that if I should start calling the tumor agents viruses that you and Tom would make the startling discovery that they didn’t belong in the virus group and start calling them agents.\(^93\)

Murphy seems to have first given public voice to his views at a meeting of the American Zoological Society in December 1925, where one of the hottest topics of discussion was Gye’s claim that he had successfully cultivated the chicken sarcoma agent.\(^94\) By this time Murphy had been working independently of Rous for nearly a decade and had built a solid reputation for himself in cancer research, notably on the role of lymphocytes, but also for further studies on the sarcoma virus.\(^95\) In Gye’s experiments, which he acknowledged as otherwise important, Murphy disputed the interpretation that the ability of subcultures of a tumour to induce sarcomas through at least five successive passages to uninfected birds was a clear indication of the growth and multiplication of the sarcoma agent.\(^96\) As he explained to journalists covering the meeting, he did not think that Gye had ‘taken sufficient precautions’ to justify his conclusions:

Gye’s work is open to different interpretations than he has placed upon it. . . . In subcultures of chicken tumors he always adds a generous supply of fresh embryonic tissue. It has long been known that embryonic tissue may assume a malignant character under the influence of the filtrate from the chicken tumour and in time these cells are capable of producing more of the active agent.\(^97\)

Murphy felt that the tumour agents were produced within the cells rather than being of extrinsic origin, and that they were ‘comparatively simple substances which belong to the field of biochemistry rather than to that of bacteriology’.\(^98\) Moreover, he stressed the importance of the agents’ ability to ‘induce permanent, inherited changes’ in their host cells, as a result of which he felt they should be differentiated from the viruses by ‘the restricted denomination of “transmissible mutagens”’.\(^99\) In this category he also included
Murphy’s transmissible mutagen posed particular problems for Andrewes who felt that the divide between it and viruses was not justified. To Murphy he wrote:

I agree with you that there is an obvious analogy between mutagen & tumour agent (and also phage); time will show if it’s a superficial analogy or a real one. I shall watch eagerly for full details about mutagen. But I don’t agree with you in [forcing] a sharp dividing line at the point x in the series below.

\[
\text{Mutagen} \quad / \quad \text{Phage} \quad / \quad \text{Tumour agent} \\
\quad / \quad / \quad / \quad / \quad / \quad / \quad \text{Other viruses} \quad \text{Pleuropneumonia} \quad \text{Bacteria}
\]

If you look at other properties of the tumour agent…. you can draw just as good a dividing line at y or at z or anywhere else you like according to the criteria you pick on. I’m much more sympathetic with [the] view that there is no very sharp dividing line anywhere in the series ….

How Murphy responded is unknown, for this letter is the last item in the archive’s files, but it does not seem that the two men found common ground. A year later Andrewes devoted an entire section of his Oliver–Sharpey lectures to ‘Murphy and transmissible mutagens’, wherein he systematically countered Murphy’s claims that transmissible mutagens were significantly different from viruses, concluding with the following note:

I have often been tempted to believe … that the Rous agent is a cell product and not a living parasite; but its analogies with other viruses are so striking that I cannot conscientiously disregard them. It is easy to understand the point of view which refuses to believe that the filtrable agent in a spontaneous tumour—or a tar-induced tumour—is a virus. But if the agent has all the properties of a virus, one can go too far in denying that it is a virus simply because it turns up in an unexpected place. If one found something with all the properties of an elephant on top of the Matterhorn, rather than deny it was an elephant one would seek to explain how it got there.

‘I’m afraid Murphy won’t love me any more after the things I’ve said about transmissible mutagens. I must send a soothing note along with his reprint’, he wrote and told Rous at the time of the lectures, and later, after they were published, mischievously inquired: ‘Do you happen to know whether a) Murphy calls the Shopiloma a tumour; b) whether he calls the Shopiloma virus a mutagen; c) whether my name is mud since I wrote the Oliver-Sharpey lectures?’

From this and other disparaging references sprinkled in his letters to Rous and from his formal writings, one can conclude that one reason why the term transmissible mutagen irked Andrewes so was that it did not signify anything really different to him. According to him the transmissible mutagen had two main properties: ‘first, the ability to direct the specific differentiation of the cell into an abnormal channel and secondly, of course, transmissibility’. Nothing in this description really contradicted the notion of what was then a virus. Even Murphy acknowledged this fact:

In common with the so-called viruses, the tumor agents are ultramicroscopic, filterable and their proliferation is intimately dependent on the presence of susceptible living cells. On the basis of such very general characters one might be justified in including these agents among the viruses.
That such ultramicroscopic beings could be transmissible was certainly not an issue, and as for the second part of Murphy’s label, there were no known properties that precluded viruses from inducing changes in their host; that is, from acting as mutagens. Indeed, the idea that viruses were among various things capable of inducing mutations had just begun to circulate in the scientific community around that time; for example, in 1936 Burnet reported the ability of a bacteriophage to induce a mutation in its host bacterium.\textsuperscript{107} What Murphy really objected to then, as he had always—witness his comments on Gye’s findings\textsuperscript{108}—was the idea of the \textit{living} nature of the sarcoma agents. But he does not seem to have satisfactorily addressed the points that Andrewes had raised in his lengthy 1931 letter.

While their years-long stand-off makes Murphy one of the most logical choices for the titular oncologist of Andrewes’s fairy story, Ewing may have been the more immediate target from the perspective of timeliness. With years of experience observing cancer patients, Ewing surely represented the prototypical cancer pathologist of those times, who held strong opinions about what cancer research should be. For one, ‘he believed that cancer research should be centered around the cancer patient’, and second, he held little regard for animal models.\textsuperscript{109} He seems a likely candidate for the role of oncologist because of a lecture he had delivered in Toronto in early 1935 in which he came out roundly against the idea of viral aetiology: ‘all the [cancer-related] phenomena observed may be explained as the result of the action of intrinsic cell products, and at no time is it necessary to introduce the idea of an extrinsic virus.’\textsuperscript{110}

This lecture stressed the very points that Andrewes had prophetically raised to Rous in a letter written shortly before, congratulating Rous on the success of his rabbit papilloma work: ‘Will the pundits think up a good reason for not calling it a true tumour?’\textsuperscript{111} Almost as if in direct reply, Ewing claimed:

\begin{quote}
When a tumour or tumour-like process is really initiated by a virus, as seems to be the case with human warts and the papillomas and fibromas of rabbits, that fact seems to be easily demonstrable, but these diseases are infectious and contagious, and they are not cancer.\textsuperscript{112}
\end{quote}

The receipt of a copy of Ewing’s lecture had spurred Andrewes to write to him, complete with apologies in advance, with ‘some comments I should like to make’, on the manuscript.\textsuperscript{113} The comments turned out to be a list, ‘in undecipherable handwriting’, of points that Andrewes disagreed with in the lecture.\textsuperscript{114} Many of these criticisms were, in fact, levelled against the ideas of Murphy, whose research Ewing had cited extensively in his arguments. ‘The evidence which has apparently convinced you that [the chicken tumour agents] are not viruses . . . seems to me to be based less on the naked facts than on Murphy’s interpretation of the facts (with which I and many others profoundly disagree)’, wrote Andrewes, adding as a specific point, ‘I know of no vigorous treatment which fowl tumour viruses withstand which other viruses won’t. (Another vision of the truth through Murphy’s spectacles).’ He concluded his note to Ewing with an invitation to share it: ‘I have no objection to your showing this letter to Murphy. He and I are old controversialists, and I hope good friends. If you do so, be fair and have Rous’ view on the other side.’\textsuperscript{115}

Even Rous on reading this letter felt that Andrewes had probably been too harsh, remarking in a private note (not shared with Ewing) that

\begin{quote}
The first I know of your attack on Ewing,—for it can be termed nothing less,—was when he sent a copy of your letter accompanied by a rather crusty note asking what I had to say
\end{quote}
to it. There was reason for him to be crusty. If there is one thing more than another that he
tries to be it is fair.

But Rous did not really have a quarrel with Andrewes’s ideas, only his manner of
presenting them, for he then went on to take a few potshots at Ewing himself:

the Toronto address hadn’t come my way before, and there followed a nip and tuck
correspondence winding up with a statement from Ewing that he wouldn’t be surprised
if some human papillomas, especially of the nose, and Paget’s disease as well, turned
out to be due to viruses. Now what do you think of that? ! Well, you needn’t think
anything for what happened next was that Ewing appeared at a . . . meeting for the
purpose of denouncing the Shope virus, the pap., the cancers emerging therefrom and
all thereto appertaining,—this a propos of nothing except some squibs [I was] firing off
about the virus in various sorts of wild rabbits…. He couldn’t help it, poor fellow; the
impulse was too strong; . . . You yourself would like Ewing (and be sorry for him).\textsuperscript{116}

Meanwhile, other than remarking to Ewing that Andrewes’s letter was ‘written with a
characteristic breeziness,’ Rous confessed that he agreed with most of the criticisms: ‘Before
reading Andrewes’ queries carefully it seemed best to re-read your paper and mark down the
points of objection which had occurred to me. On comparing this list with Andrewes’ they
check closely.’ Perhaps to temper his own remarks and simultaneously to persuade Ewing to
consider Andrewes’s point of view more carefully, he added: ‘When it comes to knowledge of
the viruses Andrewes can skate all around most people . . . I am coming to know about viruses
secondarily and that may be to some extent the case with yourself.’\textsuperscript{117}

Ewing, on the other hand, seemed to have gotten over his ‘crustiness’ toward Andrewes,
but not his fundamental disagreement on the matter of viruses and cancer, responding to
Rous: ‘I thought Andrewes’ letter was very restrained. Your own is much more subtle. I
presume it all settles down to the question, what is a virus.’\textsuperscript{118}

That last sentence gets to the heart of what was the main contention between the two
sides, with Andrewes and Rous on one side and Ewing and Murphy on the other. Here
the champions of the virus theory had a slight upper hand, because it is not entirely clear
from the writings of the cancer pathologists that they had a common understanding of the
nature of viruses or of the cancer agent, save for the fact that the latter was \textit{not} the
former. For instance, Ewing—fervently convinced that a ‘theory of a universal cancer
parasite stimulating the cell to incessant growth . . . must be ruled out of court on the
ground of no evidence’\textsuperscript{119}—likened the sarcoma agent to an enzyme, citing his
interpretation of Murphy’s work as corroboration: ‘That the active agent in chicken
sarcomas is a chemical substance resembling the class of enzymes is strongly indicated, if
not definitely proven, by the investigations of Murphy and his associates.’\textsuperscript{120}

But Ewing was in error here. Although Murphy had earlier suggested the possibility that
‘the causative agent of the chicken tumor is in the nature of an enzyme-like substance’,\textsuperscript{121} he
had definitely dismissed the possibility by the 1930s because he repeatedly observed that
‘unlike enzymes, the tumor agents essentially reproduce themselves and can be
perpetuated by passage \textit{in vivo}’.\textsuperscript{122} His own conception of the tumour agent was along
genetic lines, an explanation that also addressed the problems of explaining the biological
variability of tumours through the mechanism of mutations: ‘Rather than connected with
the cell metabolism, . . . the tumor producing mechanism in our opinion seems to be more
closely related to the function which in the cell carries the fixed characters and controls
the specific differentiation.’\textsuperscript{123}
Besides misinterpreting Murphy, Ewing’s arguments also reveal a somewhat confused understanding of the distinction between viruses and enzymes. In his lecture he had given one of his arguments against the viral nature of the cancer agent in these terms: ‘The evidence regarding multiplication indicates that the agent increases only in the presence of actively growing cells. This property is characteristic of viruses. Yet crystalline enzymes multiply rapidly in suitable substrates.’

But his reaction to Andrewes’s request that ‘I should very much appreciate the reference to the multiplication of crystalline enzymes, of which I am ignorant’ shows Ewing conflating the two terms: ‘The virus of Mosaic disease has been isolated in crystalline form, and it certainly multiplies’, he told Rous. Despite his protestations—‘You see, I am trying my best to find a cancer directly caused by a virus’—Ewing clearly grasped at any straw against a viral, in other words extrinsic, involvement in cancer. Yet another line of argument was that

the problem of the origin of tumours is wholly different from the problem of their continued growth. . . . One concerns the exciting factors, the presence of which initiates the tumour process, while the other relates to the nature of the tumour process itself. The former may be called the causal genesis, the latter the formal genesis.

Although he conceded that viruses might instigate tumours, Ewing could not imagine them being involved in the formal genesis, as the ‘Three Musketeers’ argued. Ewing vocalized his opposition publicly at Rous’s Harvey lecture, an episode that Rous described eloquently and vividly a few weeks later:

That Harvey Lecture proved far from a joke. I never laboured more for what is called a ‘definitive pronouncement.’ You know that at the end of such a lecture it is the custom for someone to arise, being bound thereto beforehand, and say pleasant things of the lecturer. This time it was Ewing, and casting my eyes about I knew it was sure to be he and was prepared for what came as the audience were not. For Ewing’s praise turned out to be the most ardent and lop-sided damnation.

Rous was not as sanguine about Ewing’s attitudes as he tried to seem in this letter. Gye offered to play peacemaker over Andrewes’s ‘attack’—‘I ought to have spotted the part which upset Ewing’, he wrote, adding: ‘I should hate anybody from England to be unjust to Ewing & Andrewes would be the last person to be unjust & wounding. If Ewing has any kindness at all for me, would you tell him from me that Andrewes was writing a mixture of fun & serious comment?’ But Rous, freshly smarting from the Harvey lecture fallout, declined, saying: ‘Your remarks on the subject of Ewing find me somewhat disposed to let him have it. He has become fanatically active in the attempt to keep the tumor problem in limbo.”

Andrewes’s account after he finally met Ewing in person underscores the impression that even if he had not been foremost in Andrewes’s mind when the fairy story was composed, Ewing would have moved up the line to first place as the prototypical ‘oncologist’ who needed to be convinced of the validity of the viral theories of cancer:

I met [Ewing] for the first time a week or two ago—with Gye. . . . A nice man but he doesn’t face facts. One remark of his I have saved up for you: ‘In Science it is always happening that pursuit of a false clue has led to the accidental discovery of important new facts. For instance look what interesting things Rous has turned up while pursuing
his mistaken ideas as to a parasitic aetiology of cancer! Now you see your life’s work in a true perspective. \(^{132}\)

**OF BARDs, PRINCE CHARMINGS AND HAPPY ENDINGS**

Andrewes’s story may lack some of the typical characters of fairy tales, but it had in Rous an essential element to ensure some measure of success for such a tale: that bard or troubadour who spreads the word about the story ensuring its survival and longevity. We know that Rous did not hesitate to share the story immediately with others besides Shope. ‘From the way in which I slip into your imagery (and bungle it) you can judge how your Christmas story was relished’, he wrote to tell Andrewes, adding:

I’ve shown it to sundry and it may well get to all in the course of time as it acquires historical value which may very well hap[pen]. It points the case and it makes to think; … I’ve sent a copy to Gasser who is in the process of understanding virus problems and he says he wants to read it again for his own uses. How much is lost because scientific journals have to be solemn. A joke can only be slipped in on the sly. \(^{133}\)

Meanwhile, however, he also played the role of bard with his own version of the tale of viruses and cancer—at his Harvey lecture where Ewing had held forth against him. Although the fairy story reached him too late to feature in his lecture, it was nevertheless ‘richly seasoned with Andrewes’. \(^{134}\) Some of the common themes between the lecture and the fairy tale include the recognition that virus–host interactions could have more outcomes than just necrosis, the notion that mutants—‘variants’ in his words—were responsible for inducing the tumours, and the idea that viruses and hosts entered a state of symbiosis. \(^{135}\)

Although it did not have one at the time of its writing, the fairy story also acquired, some 20 years after its telling, a Prince Charming. True, he was a borrowed character but given that it was Burnet’s model for lysogeny that Andrewes assimilated into his scenario of the viruses in feudal existence in the germ plasms of their host cells, the borrowing seems fitting. Burnet himself had acquired the prince in a tribute to his work on lysogeny:

[Burnet’s] investigations led to the realization that viral genes could have a life cycle in or out of a host genome. … His insight into lysogeny slept for twenty years … to be awakened after World War II by Andre Lwoff whose Prince Charming kiss brought forth as progeny the fields of virology [and] recombinant DNA. \(^{136}\)

This ‘Prince Charming kiss’ metaphor is as applicable to the case of cancer viruses as it is to the bacteriophages. When Burnet had proposed his mechanism for lysogeny (also used by Andrewes to describe the behaviour of the tumour viruses) there had been no material basis for visualizing it. But with the knowledge that genes were made of DNA, the functions of the nucleic acid and protein components of viruses were clarified and Lwoff’s definition of the prophage as ‘the form in which lysogenic bacteria perpetuate the power to produce bacteriophage’ \(^{137}\) offered a way to comprehend lysogeny. In the lysogenic state it was only the viral nucleic acid that became integrated into the bacterial genome, which meant that no entire viral particles could be seen or released upon bacterial lysis. If the viral genes were somehow stimulated to express themselves, the host cell could produce viral proteins (‘tusks’ inclusive) and duplicate viral DNA, which could, in turn, be assembled into virus particles, the production of which was ‘a lethal event’, namely, bacterial lysis in the case of bacteriophages. \(^{138}\)
Lwoff’s data and theories pertained to the bacteriophages, but, as he pointed out, ‘it would be of the utmost interest to know whether or not immunity in animals or plants may be correlated with the presence of a provirus-like material’. He also discussed the possible analogy between ‘lysogeny and some neoplastic or neoplastic-like diseases’, although there was no mention of Andrewes or his ideas. Only then did the ideas of the ‘Three Musketeers’ fighting for a revolution in cancer aetiology come to be realized. Soon thereafter, other virologists such as Renato Dulbecco—unknowingly following Andrewes’s fairy tale—explicitly drew analogies between the processes of bacteriophage lysogeny and the changes wrought by various tumour viruses in their host cells. Eventually Dulbecco showed that the DNA of a tumour-causing virus called SV40 was integrated into the genome of tumour cells. This work would garner him one-third of the 1975 Nobel Prize in Physiology or Medicine, another third of which went to Howard Temin, specifically for elucidating the mechanisms by which the Rous sarcoma virus integrated itself into the host’s genome.

The 1975 Nobel prize could qualify as a happily-ever-after for Andrewes’s fairy story in and of itself, because although not acknowledged the story had made the same predictions (in the truest sense of a scientific hypothesis) years before they were translated into reality. More recently Angela Creager, noting that cancer viruses ‘were successful in infecting biomedicine itself’, identified a triumph of much wider scope: ‘the enduring infrastructure of tumor virology … suggests a happier ending to the tale of cancer viruses than either Andrewes or Rous dared dream’.

To us, however, it is the award of the 1966 Nobel Prize in Physiology or Medicine to Rous that stands out as the most fitting happy ending not only for the fairy story but also for the long correspondence between the these men. Naturally the Nobel prize was a long-awaited vindication for Rous, who holds the record as the oldest recipient of the prize at the age of 87 years, and moreover for work done 55 years earlier. A regrettable consequence of the award so late in the day was that virtually none of the other players—allies or adversaries—were around to witness Rous’s triumph; only Andrewes, the youngest, was still living. But his unalloyed pleasure and joy on receiving news of the prize makes it as much of a happily-ever-after for him as for Rous, on which note we end our article, as we began, with an extract from one of his letters to Rous:

HURRAY! They should have done it several decades ago. What a triumph for righteousness and perceptiveness! You’ll no longer feel an inferiority complex in talking to your son-in-law. What a pity Dick [Shope] can’t share in your pleasure.

Of course you’ll go to Sweden via U.K. … Have put in an order for a red carpet & a fatted calf.

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APPENDIX 1. REPRODUCTION OF THE FAIRY STORY

A CHRISTMAS FAIRY-STORY FOR ONCOLOGISTS

Once upon a time there was a family of viruses, much like other viruses. Some of them liked mutton, others poultry. Some of them multiplied wantonly in the cells they inhabited, and smashed up their homes; others, more restrained, practiced a magic which caused their homes to proliferate. But after a while most of the homes got broken up and the viruses had to seek new ones in new hosts. These new homes they penetrated by means of the powerful tusks in their upper jaws.

Now the hosts didn’t like this business and they defended themselves in two ways. They provided themselves with weapons called antibodies which smashed the tusks of the viruses so that they couldn’t enter new cells and died of inanition and exposure. Or else they made terms with the enemy and said ‘Come right in and live in our cells. But you must practice birth-control and leave the furniture alone. If you do that you may come even into the inner sanctum of our germ plasm and be tolerated as feudal retainers from generation to generation.’*

In this feudal existence most of the viruses lost all ambition and ceased to clean their teeth, which became subject to dental caries and fell out. And after a few generations the race was quite tuskless. Some of them retained their teeth and their self-respect (like the rabbit papilloma virus) but even they were apt to become edentulous in the fat luscious cells of the domestic rabbit. Others—the poultry-loving race—didn’t bother as a rule, but were readily able to sprout tusks again whenever it seemed worth the trouble.

Now this was all very well, except for one complication. The hosts which had admitted viruses upon terms as feudal retainers had left nothing to chance. They had always built their cells with virus-proof cement. Occasionally, however, dry rot got into the walls after exposure to hydrocarbons with a phenanthrene nucleus, or a fire-work party of X-rays would cause cracks to appear. Then the young bloods would see chance for revolt. Perhaps they would run riot and smash up the home, as their ancestors did. If they did,—well it was only one cell amongst millions, and the young bloods when they found themselves homeless, perished miserably for they had no tusks to help them enter new cells. But perhaps, they would practice their ancestral proliferation-magic, and then no one could stop them. Some were cleverer at it than others, some improved with practice; and the results were neoplasms of all degrees of malignancy. Ultimately the host died and the viruses with them,—for still they didn’t know how to grow tusks. And pathologists, who thought that all viruses had tusks, studied the neoplasms and grunted into their beards ‘The parasitic hypothesis of cancer is dead.’
The hosts became alarmed at the increasing incidence of cancer and called upon the Goddess Evolution at a great religious revival. But, alas, the goddess had no interest in diseases which attack creatures after they have successfully propagated themselves, and turned a deaf ear to their prayers.

*This is Hans Andersen’s version. Grimm says they were only allowed to live a saprophytic existence in the Servant’s Hall and weren’t allowed in the cells at all. I don’t know which is right.*

C.H.A.

**Notes**


2. APS, Andrewes, letter to Rous, 6 December 1935. The reference is to Richard Edwin Shope (1901–66), an American virologist best known for his work on hog cholera and the discovery of the rabbit papilloma virus. Shope spent most of his career as a researcher at the Rockefeller Institute for Medical Research, where he was Rous’s colleague.

3. APS, Peyton Rous papers. These archives contain an extensive collection of the correspondence of Rous with both Andrewes and Gye. For a detailed discussion of the role of this correspondence in shaping Rous’s ideas and career, see E. Becsei-Kilborn, *Going against the grain: Francis Peyton Rous (1879–1970) and the search for the cancer virus* (University of Illinois at Chicago, 2003). Also see J. A. Secord, ‘How scientific conversation became shop talk’, *Trans. R. Hist. Soc.* (6) 17, 129–156 (2007) for a broader discussion of the role in informal exchanges in science.


7. For examples of the views on cancer aetiology by oncologists in the early decades of the twentieth century, see Becsei-Kilborn, *op. cit.* (note 3), pp. 110–152.


11 See Rous, op. cit. (note 9).


20 APS, Peyton Rous Collection, Rockefeller Institute: Reports for the Board of Directors, folder 1, 1911–15.


22 Rous, op. cit. (note 1), letter to Andrewes, 21 April 1953. See also Shope, op. cit. (note 9).


26 Ibid., p. 420.

27 Ibid., p. 422.

28 APS, Peyton Rous papers, Gye, William E., folder 1, 1923–25, Gye, letter to Rous, 8 November 1923.

29 Rous, op. cit. (note 28), letter to Gye, 27 December 1923.


31 Rous, op. cit. (note 21), letter to Andrewes, 21 April 1953.
32. Rous, op. cit. (note 10), letter to Gye, 19 April 1936. The table can be found in Rous, op. cit. (note 1), p. 87.


34. Gye, op. cit. (note 10), letter to Rous, 1 March 1935.

35. Rous, op. cit. (note 21), letter to Andrewes, 7 January 1953.


37. Mervyn Henry Gordon (1873–1953), a British medical researcher who spent most of his career at St Bartholomew’s Hospital, known for his studies on mumps, polio and influenza viruses as well as Hodgkin’s disease.


41. Andrewes, op. cit. (note 38), p. 3.


46. Ibid., p. 63.


53. Ibid.

54. Ibid.

55. R. O’Connor, ‘Hyena-hunting and Byron-bashing in the Old North: William Buckland, geological verse and the radical threat’, In Marsden et al. (eds), op. cit. (note 51), pp. 55–82.


57. Only relevant excerpts of the fairy story are extracted in this section; the entire story is reproduced in Appendix 1. Apart from this first instance, extracts are not identified by endnotes in the remainder of this section.


64 Rous, *op. cit.* (note 21), letter to Andrewes, 21 April 1953. The first person mentioned in this letter was Mitchell Prudden (1849–1924), an American pathologist especially known for his role in developing the New York City Board of Health, and one of the original members of the Board of Scientific Directors of the Rockefeller Institute, its first vice-president as well as the first chairman of its executive committee. The second person, James B. Murphy (1884–1950), was Rous’s colleague on much of his sarcoma work at the Rockefeller Institute, who harboured rather different ideas about the nature of the sarcoma agent, in that he did not believe it was a living virus. Murphy’s role in this story is discussed at length in a later section of this article.

65 APS, Peyton Rous papers, folder Williams, Greer, Rous, letter to Greer Williams, 4 November 1958. Rous was wrong in remembering the year of his Harvey lecture, which was 1935 and not 1934 (see Rous, *op. cit.* (note 1)).


67 Andrewes, *op. cit.* (note 45), p. 117.


69 APS, James B. Murphy papers, folder Andrewes, C. H., [1930–32], Andrewes, letter to Murphy, 22 May 1931.

70 Andrewes, *op. cit.* (note 1), letter to Rous, 28 January 1933.

71 Rous, *op. cit.* (note 1), letter to Andrewes, 20 March 1933.

72 Andrewes, *op. cit.* (note 1), letter to Rous, 11 April 1933.


79 See Sankaran, *op. cit.* (note 14), for a fuller exposition on the many parallels in the history of research on bacteriophages and cancer viruses.


81 Andrewes, *op. cit.* (note 1), letter to Rous, 6 December 1935.

82 Andrewes, *op. cit.* (note 80), p. 84. In this article Andrewes changed the metaphor from tusks to teeth.

83 Andrewes, *op. cit.* (note 36), letter to Ewing, 17 September 1935.
Emphasis added.


In contrast to five folders of correspondence between the latter pair, lasting over nearly five decades, for example, Murphy’s collection contains only one folder of letters from Andrewes dating to the early 1930s.

Andrewes, op. cit. (note 69), letter to Murphy, 1 January 1933.

Murphy, op. cit. (note 69), letter to Murphy, 30 January 1933.


Little, op. cit. (note 89). For accounts of Murphy’s contributions to the study of lymphocytes also see I. Löwy, ‘Biomedical research and the constraints of medical practice: James Bumgardner Murphy and the early discovery of the role of lymphocytes in immune reactions’, Bull. Hist. Med. 63, 356–391 (1989), and A. M. Silverstein, ‘The lymphocyte in immunology: from James B. Murphy to James L. Gowans’, Nature Immunol. 2, 569–571 (2001). After Rous ceased his work on the sarcoma virus, it was Murphy’s laboratory that kept research on the topic alive at the Rockefeller for many years (Moberg, op. cit. (note 89)).


Anon., ‘Dr. Murphy doubts cancer isolation; surgeon of the Rockefeller Institute calls Dr. Gye’s tests inconclusive’, New York Times (3 December 1925).

A. Claude and J. B. Murphy, ‘Transmissible tumors of the fowl’, Physiol. Rev. 13, 246–275 (1933), at p. 259. See also J. B. Murphy, ‘Discussion of some properties of the causative agent of a chicken tumor’, Trans. Assoc. Am. Physicians 46, 182–187 (1931), which was the first publication in which Murphy introduced the phrase ‘transmissible mutagen’.

Claude and Murphy, op. cit. (note 98), p. 261.

Andrewes, op. cit. (note 45), p. 120.

Andrewes, op. cit. (note 69), letter to Murphy, 22 May 1931. (Emphasis in original.)

Andrewes, op. cit. (note 45), p. 121.

Andrewes, op. cit. (note 1), letter to Rous, 2 May 1934.
Andrewes, *op. cit.* (note 1), letter to Rous, 19 November 1934. ‘Shopiloma’ is evidently a shorthand reference to the rabbit papilloma, discovered by Shope and later studied in detail by Rous.

Andrewes, *op. cit.* (note 45), p. 120.

Claude and Murphy, *op. cit.* (note 98), p. 258.


Murphy, as quoted in Anon., *op. cit.* (note 97).


APS, Peyton Rous Papers, Ewing, James, folder 1924–36, Andrewes, letter to Ewing, 17 September 1935. A typed copy of this letter heavily annotated by Rous indicating his thoughts on Andrewes’s comments, is filed with Ewing’s 7 October 1935 letter to Rous.


Andrewes, *op. cit.* (note 113), letter to Ewing, 17 September 1935.


Rous, *op. cit.* (note 113), letter to Ewing, 3 October 1935.

Ewing, *op. cit.* (note 113), letter to Rous, 7 October 1935.


J. B. Murphy, ‘Observations on the aetiology of tumors: as evidenced by experiments with a chicken sarcoma’, *J. Am. Med. Assoc.* 86, 1270–1271 (1926). He had also made a similar statement in a letter to a former colleague: ‘we have been able to isolate a causative agent which has every indication of being an enzyme-like body’ (Murphy, *op. cit.* (note 90), letter to Nakahara, 22 June 1928).

Claude and Murphy, *op. cit.* (note 98), p. 259.


Andrewes, *op. cit.* (note 113), letter to Ewing, 17 September 1935.

Ewing, *op. cit.* (note 113), letter to Rous, 7 October 1935. (Emphasis added.)

Ewing, *op. cit.* (note 113), letter to Rous, 9 October 1935.


Rous, *op. cit.* (note 1), letter to Andrewes, 11 January 1936. Here as in his letter to Greer Williams, *op. cit.* (note 65), Rous incorrectly dated his Harvey lecture; the events he mentioned took place in December 1935, as is corroborated by Andrewes’s letters and the published version of the Harvey lecture (Rous, *op. cit.* (note 1)).


Rous, *op. cit.* (note 10), letter to Gye, 28 December 1935.

Andrewes, *op. cit.* (note 49), letter to Rous, 22 October 1936.

Rous, *op. cit.* (note 1), letter to Andrewes, 11 January 1936. The reference is to Herbert Gasser (1888–1963), an American physiologist and a recipient of the 1944 Nobel Prize for Physiology or Medicine for his contributions to the function of nerve fibres. At the time of this letter, Gasser was the newly appointed director of the Rockefeller Institute.

135 Rous, op. cit. (note 1), pp. 86, 102 and 112 respectively.


139 Lwoff, op. cit. (note 137), p. 323.

140 Ibid., p. 325.


143 Creager, op. cit. (note 4), p. 262.


145 The Nobel Prize in Physiology or Medicine (see http://www.nobelprize.org/nobel_prizes/medicine/; accessed 11 December 2015).

146 In chronological order: Ewing had died in 1943, Murphy in 1950 and Gye in 1952.

147 APS, Peyton Rous papers, Nobel Prize—Congratulatory letters (1966–67), folder A, Andrewes, letter to Rous, 14 October 1966. Rous’s son-in-law, married to his oldest daughter Marion, was Alan Hodgkin, the British biophysicist and neuroscientist, a winner of the 1963 Nobel Prize in Physiology or Medicine (see http://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/) for his contributions to understanding the nervous cell membranes. Shope had succumbed to cancer on 2 October 1966, poignantly, mere days, even hours, before the Nobel announcement.