

(A)Historical Science

Arturo Casadevall,^a Ferric C. Fang^b

Department of Molecular Microbiology & Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA^a; Departments of Laboratory Medicine and Microbiology, University of Washington School of Medicine, Seattle, Washington, USA^b

In contrast to many other human endeavors, science pays little attention to its history. Fundamental scientific discoveries are often considered to be timeless and independent of how they were made. Science and the history of science are regarded as independent academic disciplines. Although most scientists are aware of great discoveries in their fields and their association with the names of individual scientists, few know the detailed stories behind the discoveries. Indeed, the history of scientific discovery is sometimes recorded only in informal accounts that may be inaccurate or biased for self-serving reasons. Scientific papers are generally written in a formulaic style that bears no relationship to the actual process of discovery. Here we examine why scientists should care more about the history of science. A better understanding of history can illuminate social influences on the scientific process, allow scientists to learn from previous errors, and provide a greater appreciation for the importance of serendipity in scientific discovery. Moreover, history can help to assign credit where it is due and call attention to evolving ethical standards in science. History can make science better.

The history of science bores most scientists stiff.

—Sir Peter Medawar (1)

One of the unique experiences of being human is to have a history. The ability to recount the past and pass it on to future generations is made possible by the symbolic language unique to our species. Most human history has been conveyed by oral narratives and legends. However, the invention of writing allowed history to acquire a new permanence. Herodotus, who lived in Greece during the 5th century B.C.E., is generally regarded as the first historian who attempted to systematically organize and analyze information. (There are others who regard Thucydides as the first true historian and Herodotus as the “first liar” for getting so many of his facts wrong [2].) Personal histories define individuals, while communal histories define groups and nations. In some areas of human endeavor, such as law and politics, history is essential for interpreting and understanding the present, and competing versions of history are often critical points of contention. However, science is a human endeavor in which the study of its own history plays a less prominent role. This is evidenced by the scant attention paid to history during the scientific training process, the ahistorical style of most scientific literature, and the separation of science and the history of science as academic disciplines. As part of our exploration of the state of current science that includes descriptive (3), mechanistic (4), important (5), specialized (6), diseased (7), competitive (8), and field (9) science, we now examine the importance of history in the scientific process and the consequences of its neglect.

Dictionaries describe history as a chronological record of significant events, often including an explanation of their causes (10). From such a definition, the history of science would include the Copernican revolution, Newton’s *Principia*, the Darwin-Wallace theory of evolution, and the theory of relativity. Major events in the history of science are widely known and well documented, although the intellectual and experimental struggle required for discovery may not be as well appreciated. For example, while all scientists are aware of the Copernican revolution and Galileo’s struggle with the Catholic Church, the scientific arguments made

in favor of a geocentric universe, such as the inability to detect stellar parallax (11), are less common knowledge. Although major scientific discoveries eventually become accepted as fact, the hard-fought struggles to obtain this understanding tend to fade with the passage of time.

Why do most scientists ignore the history of science? Assuming that Sir Peter is correct in saying that “the history of science bores most scientists stiff,” it is perhaps not difficult to explain the limited interest that most scientists take in history. Science by its very nature seeks to push back the boundaries of the unknown—the border between the known and unknown is far more interesting to scientists than what happened in the past. Although most students in the biological sciences learn about the discoveries of Darwin, Mendel, and Watson and Crick, it is fair to say that historical training is not a major part of the undergraduate or graduate science curriculum. Very few scientific fields have an accessible historical literature to supplement scientific training. While some students may have learned additional science history from courses that consider classic papers, most learn the history of their chosen field of study from their laboratory mentor or from review articles that emphasize historical aspects of discovery. Human aspects of scientific discovery, such as scientific rivalries and their effect on science, are generally not discussed in formal articles. Rather, such information is maintained within fields by an oral tradition consisting largely of gossip, anecdote, and rumor. One can master a scientific topic without having the least idea of how the knowledge was obtained. For example, it is possible to describe the central dogma of molecular biology from transcription to

Accepted manuscript posted online 14 September 2015

Citation Casadevall A, Fang FC. 2015. (A)Historical science. *Infect Immun* 83:4460–4464. doi:10.1128/IAI.00921-15.

Editor: A. J. Bäuml

Address correspondence to Arturo Casadevall, acasade1@jhu.edu.

Copyright © 2015, American Society for Microbiology. All Rights Reserved.

The views expressed in this Editorial do not necessarily reflect the views of the journal or of ASM.

translation in excruciating detail without having to mention a single scientist's name. In this regard, science differs from politics, law, economics, or most social sciences, in which the history of events is essential for understanding the field. For example, it is impossible to understand the state of race relations in the United States without considering the history of slavery, civil war, reconstruction, segregation, and civil rights. In contrast to other intellectual pursuits, science can be viewed as being either privileged or disadvantaged because it has the luxury of neglecting its history.

The scientific literature is deliberately ahistorical. In a lecture titled "*Is the Scientific Paper a Fraud?*," Medawar also noted that the format of a conventional scientific paper consisting of an introduction, description of methods, results, and discussion implies a logical inductive process that is completely alien to how most science is actually done (12). Carmody expanded upon this point by observing that research papers not only idealize the scientific process but also drain it of the passion of discovery (13). Perhaps this has always been the case. When Elie Metchnikoff described his discovery of phagocytosis in starfish larvae in a research journal (14), he drily reported the following:

The reactive phenomena ensuing on artificial injuries may be readily observed in the much larger larvae, the *Binpinaria astrigera*. . . If a delicate glass tube, a rose-thorn, or a spine of a sea urchin be introduced into one of these larvae, the amoeboid cells of the mesoderm collect around the foreign body in large masses easily visible with the naked eye.

Yet, the historical recollection of the events in his biography (15) paints a much different picture:

One day when the whole family had gone to a circus to see some extraordinary performing apes, I remained alone with my microscope, observing the life in the mobile cells of a transparent starfish larva, when a new thought suddenly flashed across my brain. . . I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts. . . I was too excited to sleep that night in the expectation of the result of my experiment.

Medawar's criticism of the scientific literature resonates in the present day with additional profound and disturbing implications. As any working scientist knows, the process of scientific discovery is messy and often involves dead ends, chance, and being in the right place at the right time. At a minimum, the conventional format of a scientific paper distorts history by creating a narrative for scientific discovery that is different from what actually occurred. Howitt and Wilson recently revisited the question of whether writing a scientific paper in the current accepted style was itself a fraudulent act. These authors concluded that "doing science and communicating science are quite different things" and noted that little had changed since Medawar's provocative essay (16). Perhaps it is of even greater concern that the "winner take all" reward system of science and the pressure to demonstrate novelty may create perverse incentives for authors to overemphasize the novelty of their own work and fail to appropriately cite the contributions of others or selectively cite publications that support their conclusions (17, 18). Such historical neglect, whether inadvertent or purposeful, can misrepresent and bias the scientific record.

In some respects, it is an advantage that science can convey its subject matter without having to consider history. This means that science, unlike other disciplines (or the legal system [19]), is not shackled to the misinterpretations of the past. While history demands that facts be interpreted in context, scientists are wary of interpretations that are difficult to validate or falsify. Instead, untethered scientific knowledge is independent of history and can serve as a platform for further research. Scientists do not need to consider the contentious emergence of the heliocentric theory to accurately deliver probes to Mars, Ceres, and Pluto. However, there are significant costs when science neglects its history. The history of science is replete with instances in which facts and research were forgotten and later rediscovered. For example, the changes in cross-striated muscle during contraction were known in the 19th century but forgotten, only to be rediscovered in the mid-20th century (20). The vertical optical fasciculus was described by the neuroanatomist Wernicke in 1881 but later disputed and forgotten until the recent work of Wandell and colleagues (21). Moreover, scientists who are concerned with only the facts and not the process miss out on the rich human drama of perseverance, serendipity, inventiveness, and conflict that characterizes the history of science. It is often such details that are most interesting to a nonspecialist, which in turn facilitates teaching and the engagement of the general public with science. The omission of the history of discovery from scientific papers may thus serve to perpetuate the barrier between scientists and the public whom they serve and depend upon for support.

To neglect history and accept the scientific literature as record is in fact to embrace a false narrative. The absence of a historical perspective of science can create a disconnect between perception and reality. In a seminal essay (22), Brush jokingly suggested that the history of science should be "X-rated" because

Young and impressionable students at the start of a scientific career should be shielded from the writings of contemporary science historians. . . because of violence to the professional ideal and public image of scientists as rational, open-minded investigators, proceeding methodically, ground incontrovertibly in the outcome of controlled experiments, and seeking objectively for the truth.

However, the serious subtext of this statement is that "the history of science may be used to challenge the supposedly truth-seeking nature of science" (23). This is a devastating criticism because it implies that scientists who ignore the discrepancies between the real and idealized views of science may also undermine their legitimacy as objective and trustworthy authorities on the realities of the natural world.

Why scientists should care about the history of science. The history of science is important because it highlights the ingenuity of earlier scientists and provides a map to connect current pathways of discovery with the past. To this, we add five reasons why scientists should pay greater attention to history.

(i) **Science is influenced by historical and social factors.** The great pathologist Rudolf Virchow rejected the germ theory of disease because his passionate concern for social justice led him to attribute infectious diseases to poverty rather than to microbes. He actually had a point, but this example shows how science is not a purely objective endeavor that stands apart from society but rather that science and culture profoundly influence each other.

This is most readily appreciated from a historical perspective. The historian may also be able to appreciate broad historical trends that are inapparent to a scientist. For example, the British philosopher Stephen Toulmin has written of the “Alexandrian Trap,” in which scientists in the 1st and 2nd centuries C.E. became increasingly specialized and focused on technology, losing sight of the bigger questions (24). Historians can help scientists to avoid this conceptual trap in the modern era by illuminating the grand arc of scientific discovery and the importance of basic research.

(ii) History allows scientists to learn from previous errors. Errors are an inescapable part of science (25). The history of science can help to show how investigators may be led astray and how the process of discovery can be improved. The historian James Atkinson has observed that scientists pay little attention to “the experiments that failed, the approaches that did not work out, the speculations without sound empirical support, and the metaphysical underpinnings of the work that did not appear in print” (26). However, such failures are the purview of historians, and scientists can learn a great deal from their insights.

(iii) A historical perspective provides a greater appreciation of how discoveries occur. Kuhn’s seminal work on scientific revolutions used history to understand how discoveries occur and come to be accepted (27). In fact, history is essential for understanding how science advances, but the scientific literature does a poor job of documenting critical events in the process of discovery. For example, scientific papers seldom mention the critical role of chance in discovery. As a case in point, we consider the association of *Helicobacter pylori* with peptic ulcer disease, a discovery that changed the treatment of this common disease and was recognized by the Nobel Prize in Physiology in 2005. In their landmark paper, Marshall and Warren paid tribute to the role of serendipity in a single sentence: “At first plates were discarded after 2 days, but when the first positive plate was noted after it had been left in the incubator for 6 days during the Easter holiday, cultures were done for 4 days” (28). Other than this casual reference to the religious calendar, the role of chance is not mentioned elsewhere in the paper. Marshall later acknowledged that prolonged incubation due to the holiday was a critical event leading to their landmark discovery. Decades of observations had suggested the presence of bacteria in stomach lesions, but these observations could not be validated experimentally because the slow-growing organism had not been successfully cultivated. The ability to grow *H. pylori* from stomach tissue allowed Marshall to establish causality in his now-famous self-experimentation that fulfilled Koch’s postulates. A greater appreciation of the role of chance and serendipity in discovery (29) could eventually result in reforms to promote transformative curiosity-driven research as opposed to an exclusive emphasis on hypothesis-driven and translational forms of research (30, 31).

(iv) History can give credit where it is due. Many alternative histories of science may emerge when scientists compete for rewards such as positions, prizes, and funding. Consider the discovery of the antibiotic streptomycin. Scientific papers tell us the origin of the compound, the properties of the molecule, and the spectrum of antimicrobial activity. However, underlying these cold facts is the struggle of a junior partner, Albert Schatz, for recognition and the efforts by a senior partner, Selman Waksman, to deny him that credit (32–34). Although the discovery of streptomycin was honored with a Nobel Prize, the committee never considered the contribution of Schatz, the graduate student who

actually made the discovery while working in a basement laboratory. We have previously argued that the Nobel Prize often assigns disproportionate credit to certain individuals while neglecting the contributions of others (35), and the Schatz-Waksman controversy is but one example. As professional recognition is the currency of science, history can play an invaluable role in setting the record straight.

(v) History reveals evolving ethical standards in science. The history of science is essential for teaching about ethical behavior in science. The sanitized literature of scientific discovery often fails to detail ethical considerations, and it is striking to consider how scientific ethical standards have evolved over time. History has allowed us to see how Pasteur’s human trials, the Tuskegee and Guatemalan syphilis experiments, and the unauthorized appropriation of Henrietta Lacks’ cells are now considered ethical transgressions (36–39), which underscores that the obligations of science to society must undergo continuing reevaluation to ensure that science remains a force for good in the world.

How to bring more history to science. We conclude by making a few recommendations to enhance the awareness of history among scientists.

(i) Recognizing science historians. The scientific culture currently rewards priority and importance in discovery (5, 40), but there is little recognition for those who chronicle and interpret the human stories behind those discoveries. Although historians of science are recognized within their own field, they are too often regarded as curiosities by scientists. Scientific recognition that science historians and journalists have a critical role in the scientific enterprise will help to elevate the value of history in science and encourage students to take an interest in these fields.

(ii) Promoting history in scientific societies. Many scientific organizations, such as the American Society for Microbiology, contain groups that are focused on history, such as the Center for the History of Microbiology/ASM Archives (CHOMA). Such groups play a critical role in preserving the past and are largely maintained by a dedicated set of history-minded individuals. The efforts of such groups should be encouraged, supported, and made more visible. Meetings, conferences, and publications provide ample opportunities to provide historical perspectives on key scientific topics and ensure continuity between the scientific past and present. Science historians and scientists alike could benefit from greater interaction and cross-fertilization.

(iii) Promoting history in scientific courses and literature. The history of science can be a powerful tool to teach and promote science. In the early 20th century, Paul De Kruif’s *Microbe Hunters* helped to inspire a generation of scientists to pursue problems in microbiology (41). One mechanism to enhance the appreciation of the history of science is to combine historical aspects of discovery with the didactic presentation of scientific information. For example, a course on nucleic acids could be supplemented by historical readings on the subject and include such material as Watson’s *The Double Helix: a Personal Account of the Discovery of the Structure of DNA* (42), Judson’s *The Eighth Day of Creation: Makers of the Revolution in Biology* (43), and Edwin Chargaff’s reminiscences on the critical discoveries that first elucidated DNA structure (44). The injection of history, with its inevitable human foibles and drama, can add interest to any course and help to stimulate discussions about how discoveries come about and what

constitutes ethical behavior. Similarly, journals could encourage more historical articles, perhaps pairing historians with scientists to document the process of discovery and encourage interactions between these disciplines. Placing new findings in the context of historical questions and discoveries can help make science more interesting to the general public. Nonscientists are often more engaged by the human history of discovery than by stark scientific facts. A greater emphasis on the historical process of discovery could also enliven courses, journal clubs, seminars, and scientific papers.

(iv) Assuring historical accuracy in scientific publications.

The scientific literature has been highly formulaic for many decades. In contrast to the papers of the early 20th century, which often provided considerable background on the problems being addressed, publications today are terse and often limited in word number and the space that they can occupy in journals. As research publications are increasingly accessible in electronic format, space limitations have become less of a concern. This should allow journals to relax restrictions on word counts that prevent historical discussions and lead to inadequate citation of the relevant literature. Given that citations are increasingly used as a measure of scientific impact, removing artificial restrictions on reference list length will help to ensure that authors are appropriately credited for their work. Perhaps some journals could introduce a small “serendipity box” where authors could tell the reader how a particular discovery came about. For example, although the role of serendipity in the discovery of phenotypic switching in *Cryptococcus neoformans* (45) was briefly alluded to in the paper, more could have been said. For that paper, the serendipity box might have stated:

This project began when strange colony morphologies were observed on agar plated with a liquid culture that had been inadvertently forgotten in a walk-in refrigerator. Although contamination was initially suspected, the colonies were shown to be *C. neoformans*, which prompted a search for the conditions that promoted such phenomena. The precedent of phenotypic switching in *Candida albicans* led the authors to specifically test whether the unusual morphologies represented a similar mechanism in *C. neoformans*.

Those few words pay tribute to the importance of serendipity and chance and provide a truthful account of how the finding came to be recognized that also acknowledges critical prior observations made with *Candida albicans*. This anecdote illustrates Pasteur’s quote that “chance favors the prepared mind,” since the knowledge of the phenomenon in another system encouraged pursuit of the observation. There is a strong lore in microbiology about forgotten culture plates leading to discovery. We note that culture plates kept past their time led to Nobel prizes for the discoveries of penicillin and *Helicobacter pylori*. Perhaps the role of serendipity is minimized in today’s literature because it is contrary to the prevailing hypothesis-driven models of discovery, and giving credit to chance takes it away from the investigators. In fact, investigators often acknowledge the role of serendipity in discovery once a finding is accepted as important and credit is assured. It is time for the scientific literature to more truthfully represent the process of discovery and to reinforce the notion that honesty is essential to the quest for truth in science.

Science is more than a disembodied collection of facts. It is a uniquely human construct, a detailed and interconnected understanding of the natural world based on innumerable observations and contributions from individuals spanning thousands of years. History can help to keep science honest, with a keen sense of where it has been and where it is going. As Darwin observed, “Great is the power of steady misrepresentation—but the history of science shows how, fortunately, this power does not endure long” (46).

REFERENCES

1. Medawar PB. 1996. The strange case of the spotted mice and other classic essays on science. Oxford University Press, Oxford, United Kingdom.
2. Momigliano A. 1958. The place of Herodotus in the history of historiography. *History* 43:1–13. <http://dx.doi.org/10.1111/j.1468-229X.1958.tb02501.x>.
3. Casadevall A, Fang FC. 2008. Descriptive science. *Infect Immun* 76:3835–3836. <http://dx.doi.org/10.1128/IAI.00743-08>.
4. Casadevall A, Fang FC. 2009. Mechanistic science. *Infect Immun* 77:3517–3519. <http://dx.doi.org/10.1128/IAI.00623-09>.
5. Casadevall A, Fang FC. 2009. Important science—it’s all about the SPIN. *Infect Immun* 77:4177–4180. <http://dx.doi.org/10.1128/IAI.00757-09>.
6. Casadevall A, Fang FC. 2014. Specialized science. *Infect Immun* 82:1355–1360. <http://dx.doi.org/10.1128/IAI.01530-13>.
7. Casadevall A, Fang FC. 2014. Diseased science. *Microbe Mag* 9:390–392.
8. Fang FC, Casadevall A. 2015. Competitive science: is competition ruining science? *Infect Immun* 83:1229–1233. <http://dx.doi.org/10.1128/IAI.02939-14>.
9. Casadevall A, Fang FC. 2015. Field science—the nature and utility of scientific fields. *mBio* 6:e01259-15. <http://dx.doi.org/10.1128/mBio.01259-15>.
10. Merriam-Webster. <http://www.merriam-webster.com/dictionary/history>.
11. Hirschfeld AW. 2001. Parallax: the race to measure the cosmos. W.H. Freeman, New York, NY.
12. Medawar P. 1963. Is the scientific paper a fraud? *Listener* 70:377–378.
13. Carmody J. 2001. Celebrating science. *Nature* 412:383. <http://dx.doi.org/10.1038/35086659>.
14. Metchnikoff E. 1893. Lectures on the comparative pathology of inflammation, Kegan Paul, Trench, Trübner & Co., Ltd., London, United Kingdom.
15. Metchnikoff O. 1921. Life of Elie Metchnikoff, 1845–1916. Constable, London, United Kingdom.
16. Howitt SM, Wilson AN. 2014. Revisiting “Is the scientific paper a fraud?”: the way textbooks and scientific research articles are being used to teach undergraduate students could convey a misleading image of scientific research. *EMBO Rep* 15:481–484. <http://dx.doi.org/10.1002/embr.201338302>.
17. Committee on Science Engineering and Public Policy. 1995. On being a scientist: responsible conduct of research. National Academy Press, Washington, DC.
18. Sawin VI, Robinson KA. 16 June 2015. Biased and inadequate citation of prior research in reports of cardiovascular trials is a continuing source of waste in research. *J Clin Epidemiol* <http://dx.doi.org/10.1016/j.jclinepi.2015.03.026>.
19. Cornell University Law School. Stare decisis. Cornell University Law School, Ithaca, NY. https://www.law.cornell.edu/wex/stare_decisis.
20. Galler S. 2015. Forgotten research from 19th century: science should not follow fashion. *J Muscle Res Cell Motil* 36:5–9. <http://dx.doi.org/10.1007/s10974-014-9399-4>.
21. Yeatman JD, Weiner KS, Pestilli F, Rokem A, Mezer A, Wandell BA. 2014. The vertical occipital fasciculus: a century of controversy resolved by in vivo measurements. *Proc Natl Acad Sci U S A* 111:E5214–E5223. <http://dx.doi.org/10.1073/pnas.1418503111>.
22. Brush SG. 1974. Should the history of science be rated X?: the way scientists behave (according to historians) might not be a good model for students. *Science* 183:1164–1172. <http://dx.doi.org/10.1126/science.183.4130.1164>.
23. Burian RM. 1977. More than a marriage of convenience: on the inextricability of history and philosophy of science. *Philos Sci* 44:1–42. <http://dx.doi.org/10.1086/288722>.
24. Toulmin S. 1974. The Alexandrian trap. *Encounter* 42:61–72.
25. Casadevall A, Steen RG, Fang FC. 2014. Sources of error in the retracted scientific literature. *FASEB J* 28:3847–3855. <http://dx.doi.org/10.1096/fj.14-256735>.

26. Atkinson JW. 1979. The importance of the history of science to the American Society of Zoologists. *Am Zoologist* 19:1243–1246.
27. Kuhn TA. 1962. The structure of scientific revolutions. University of Chicago Press, Chicago, IL.
28. Marshall BJ, Warren JR. 1984. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* i:1311–1315.
29. Meyers MA. 1995. Glen W. Hartman lecture. Science, creativity, and serendipity. *Am J Roentgenol* 165:755–764.
30. Fang FC, Casadevall A. 2010. Lost in translation—basic science in the era of translational research. *Infect Immun* 78:563–566. <http://dx.doi.org/10.1128/IAI.01318-09>.
31. Botstein D. 2012. Why we need more basic biology research, not less. *Mol Biol Cell* 23:4160–4161. <http://dx.doi.org/10.1091/mbc.E12-05-0406>.
32. Lawrence PA. 2002. Rank injustice. *Nature* 415:835–836. <http://dx.doi.org/10.1038/415835a>.
33. Schatz A, Robinson KA. 1993. The true story of the discovery of streptomycin. *Actinomycetes* 4:27–39.
34. Pringle P. 2012. Experiment eleven: deceit and betrayal in the discovery of the cure for tuberculosis. Bloomsbury UK, London, United Kingdom.
35. Casadevall A, Fang FC. 2013. Is the Nobel Prize good for science? *FASEB J* 27:4682–4690. <http://dx.doi.org/10.1096/fj.13-238758>.
36. Jones JH. 1981. Bad blood: the Tuskegee syphilis experiment. The Free Press, New York, NY.
37. Geison GL. 1995. The private science of Louis Pasteur. Princeton University Press, Princeton, NJ.
38. Skloot R. 2010. The immortal life of Henrietta Lacks. Broadway Books, New York, NY.
39. Rodriguez MA, Garcia R. 2013. First, do no harm: the US sexually transmitted disease experiments in Guatemala. *Am J Public Health* 103:2122–2126. <http://dx.doi.org/10.2105/AJPH.2013.301520>.
40. Casadevall A, Fang FC. 2012. Winner takes all. *Sci Am* 307:13. <http://dx.doi.org/10.1038/scientificamerican0812-13>.
41. De Kruif P. 1926. Microbe hunters. Harcourt, Brace and Co., New York, NY.
42. Watson JD. 1968. The double helix: a personal account of the discovery of the structure of DNA. Atheneum, New York, NY.
43. Judson HF. 1979. The eighth day of creation: makers of the revolution in biology. Simon and Schuster, New York, NY.
44. Chargaff E. 1974. Building the tower of babble. *Nature* 248:776–779. <http://dx.doi.org/10.1038/248776a0>.
45. Goldman DL, Fries BC, Franzot SP, Montella L, Casadevall A. 1998. Phenotypic switching in the human pathogenic fungus *Cryptococcus neoformans* is associated with changes in virulence and pulmonary inflammatory response in rodents. *Proc Natl Acad Sci U S A* 95:14967–14972. <http://dx.doi.org/10.1073/pnas.95.25.14967>.
46. Darwin C. 1859. On the origin of species by means of natural selection. John Murray, London, United Kingdom.