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Research Commentary

From Gutenberg to Open Science: An Unfulfilled Odyssey

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ABSTRACT With the almost global availability of the Internet comes the expectation of universal accessibility to knowledge, including scientific knowledge-particularly that generated by public funding. Currently this is not the case. In this Commentary we discuss access to this knowledge, the politics that govern peer review and publication, and the role of this knowledge as a public good in medicine.

Gutenberg's invention of the printing press in 1440 opened an avenue for the distribution of scholarly information to the entire world. The scientific literature first appeared in 1665 with *Le Journal des Sçavans* followed in the same year by *Philosophical Transactions*. Today there are more than 5000 scientific publishing companies, 25,000 journals and 1.5 million articles published/year generating revenue of $25 billion USD.

The European Union and the Organization for Economic Cooperation and Development have argued for open access (OA) to scientific data for all publicly funded research by 2020 with a similar initiative in the USA via the Fair Access to Science and Technology Research Act (FASTR). However, OA to published science is but one step in this odyssey. If the products of science are not openly available then it can be argued that the norms of science as defined by Merton including "universalism" and "communalism" have yet to be accomplished. Nowhere is this more apparent than in the delivery of medicines to the poor and for rare diseases, the attempts to privatize human genetic information and, not least, dealing with the challenges of antibiotic resistance and new disease pandemics exacerbated by climate change. Drug Dev Res 78 : 3–23, 2017.

Key words: open access; open science; metrics; impact; publications; predatory publishing; drug costs; rent seeking

INTRODUCTION

"I propose that society first agree on a simple, guiding principle: all scientific discoveries first constitute a public good and only second are the property of individual scientists, institutions or countries. Agree on this, and it follows that anything that impedes the sharing of discoveries—either by prolonging the time or complicating the process of disseminating scientific outputs—should be eliminated entirely. We should not be satisfied with anything less". Aled Edwards [2016].

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In 1517, Martin Luther started a theological revolution by nailing a printed copy of the first Ninety-Five Theses to a German church door. Courtesy of Gutenberg's printing press Luther had multiple copies of his theses available for open dissemination.

Today a major fraction of the scientific literature still remains unavailable behind pay walls, constituting a significant barrier to both scientific progress and to the public understanding of science. To fulfill the norms of science as defined by Robert Merton it will be necessary to move towards complete open publication in science [Merton, 1942a]. Exactly this has been proposed by the European Union to ensure that by 2020 ALL publicly funded scientific papers published in Europe will be made free to access [Guidelines On open Access to Scientific Publications, 2016]. The US Fair Access to Science and Technology Research Act [FASTR] of 2015 makes comparable recommendations [Fair Access to Science and Technology Research Act, 2016].

A logical economic argument can be made to justify these goals, as the current publication system represents a less than optimal use of public resources where taxpayers who fund the research then have to pay to access its results not only through subscriptions, but also sometimes with additional publication costs amounting to "double dipping" [Ayris et al., 2015].

As defined by Merton [1942a] the norms of science include the concepts of:

- *Universalism*: Claims of scientific truth are independent of the personal or national qualities or origins of their discoverers.
- *Communalism*: (originally formulated as *"communism"* by Merton) whereby the findings of science are products of social collaboration and are assigned to the community.

Merton was not, of course, unaware that these concepts were ideals that have, not infrequently, been violated and continue to be violated. However, these two concepts do form the foundation of open science requiring in turn the necessity of open publication and dissemination of scientific discoveries and their applications.

Why Publish?

Although the primary reason to publish scientific findings should be the dissemination of knowledge to the global population, most authors when asked will state that career advancement together with enhancing the prospects for research grant support is the primary reason to publish. *"Publish or Perish"* was first stated in an academic sense in the 1940s by Logan Wilson in a book entitled: *"The Academic Man: A Study In the Sociology of a Profession"* [Wilson, 1942; Garfield, 1996a]; Wilson was a former student of Merton. Today *"Publish or Perish"* is, unfortunately, of particular importance in a world where the struggle for jobs and research funding is increasingly competitive. Alberts et al. [2014] have raised serious concerns, with the USA as the example, about the current hypercompetitive nature of research with the low success rate of NIH grants resulting in scientists spending more time writing and revising applications than actually thinking about and doing the science. Such an environment hampers innovation and results in short term thinking and a conservative approach to research [Alberts et al., 2014]. In a conversation with Elizabeth Dzeng [2014], Sydney Brenner, Nobel Prize winner in Physiology or Medicine, 2002, expressed concerns over several issues related to the evaluation and funding of science and stated: *"—it's not publish or perish, it's publish in the okay places [or perish"*: a view recently reemphasized by Tantin [2016].

It has been argued vigorously that the pressure to publish actually reduces quality; however, despite, or perhaps because of, the availability of sophisticated search engines information overload is a serious problem with, for instance PubMed providing access to over 20 million published articles. A 2010 estimate indicated that 50 million articles had been published [Jinha, 2010]. Furthermore, in some disciplines as high as 90% of the published papers are never cited, not even by the authors, thus raising the question [Remler, 2014] *"Do we need to re-examine how scientific data is made available?"* Almost 30 years earlier Rennie [1986] stated: *"There are scarcely any bars to eventual publication. There seems to be no study too fragmented, no hypothesis too trivial, no literature citation too biased or too egotistical, no design too warped, no methodology too bungled, no presentation of results too inaccurate, too obscure, and too contradictory, no analysis too self-serving, no argument too circular, no conclusions too trifling or too unjustified, and no grammar and syntax too offensive for a paper to end up in print"*. Similarly, in 2006 Jennings [2006] stated: *"Whether there is any such thing as a paper so bad that it cannot be published in any peer reviewed journal is debatable"*? Clearly little has changed and, most likely, is far worse given the continued expansion in the number of journals.

Linked to these questions is: *"How should the impact of a published work be judged*?" Traditionally impact has been based on the *"Impact Factor"* (IF) of the journal, the Journal Impact Factor, or JIF, in

which the paper was published, but this may not reflect the impact of that specific paper. With the increasing availability of *"open access (OA)"* perhaps article downloads would be a better indicator? Furthermore, despite the growth in the number of journals another major concern for scientists is the frequently long delay that occurs between submission of a manuscript and its publication. The need to *"publish or perish"* has stimulated the appearance of opportunistic publishers, sometimes with fraudulent intent, to provide fast-track pay-to-publish services via what have been termed *"predatory"* and *"high-jacked"* journals, thus opening a potential *"Publish & Perish"* trap [Beall, 2016a,b,c]. Recently new approaches to providing access to data have been launched that allow the posting of manuscripts online and for feedback to be received, revisions made and ultimate submission to peer-reviewed journals.

The Oligopoly of the Publishing World

As reviewed by Larivière *et al*., [2015] academic publishing, as for other industries, has undergone major changes over the past 50 years: as a result of mergers and acquisitions just five publishing houses account for greater than 50% of articles published in the natural and medical sciences and the social sciences and humanities fields. As a result of this near monopoly, the "for profit" companies have enjoyed increased profits with total revenue for the English-language scholarly and scientific journals being approximately $10.0 billion USD, but for the broader science and technology publishing market an estimate of $25.2 billion (Ware and Mabe, 2015). There are, as outlined below, real costs for all publishing companies and, arguably, the so-called prestige and comparatively expensive journals serve science by highlighting important work (Dylla, 2016); however, as argued by Dylla, the "for profit" publishing industry has neither modified its business model fast enough nor has it convincingly promoted to its customers the true value that the industry brings to the advancement of science (Dylla, 2012).

The increasing cost of library subscription for journals has placed an ever-increasing burden on the budgets of academic libraries that have been exacerbated by budget cuts in a stringent economic environment. Despite the rising importance of the Internet, the five publishers, Reed-Elsevier, Sage, Springer-Nature, Taylor & Francis and Wiley-Blackwell have maintained their dominance [Krisch, 2015]. Nonetheless, OA journals like those published by BioMed Central (owned by Springer Nature), and PLoS (Public Library of Science) have flourished since they were launched in 2000 and 2003 respectively. PLoS now publishes 7 journals with an output of close to 30,000 articles/year [Van Noorden, 2013a]. PLoS was co-founded in 2000 by Eisen, a molecular biologist at the University of California, Berkeley, with the Nobel Prize laureate and former Director of the NIH, Harold Varmus. Eisen has stated: *"We are working to evolve all of PLOS towards a world where papers are only rejected when they are scientifically invalid"* [Van Noorden, 2013a].

There are non obvious costs for subscription-based publishers that include the costs of running editorial offices, editing services and finding peer reviewers; in addition, the lower acceptance rate for a prestigious journal may also increase the cost for publishing accepted articles; the cost would be still higher if the reviewers were also paid for their current *pro bono* services. For these reasons the cost of publishing a scientific paper is both highly variable and extremely controversial [Van Noorden, 2013a]. It is estimated that each article published by the subscription-based major publishers brings in a revenue of $5,000 with an average cost of $3000 to $4000, whereas that for an OA publication varies from as low as $1,350 to $2,250 for BioMed Central and PLoS to as high as $2,900 for the same publishers [Van Noorden, 2013a]. However, a 2012 survey conducted by Solomon and Björk [2012] provided a range of $8.0- $3,900 with an average of approximately $900 for fee-charging OA journals and also concluded that OA journals indexed in *Web of Science* and/or *Scopus* were approaching the same scientific impact and quality as their subscription counterparts [Bjork and Solomon, 2012]. In 2012 PLoS reported a surplus of US$7 million on net revenues of $34.5 million [Van Noorden, 2013b]. Nonetheless, in 2014, OA journals accounted for only 5% of the total journals market that was estimated to be $10 billion. The costs of publishing have been largely avoided by those in fields such as mathematics, physics and computer science where it is common to post pre- and post-review articles on servers such as *arXiv* at the cost of about $10/article [Van Noorden, 2013a].

The case for open access is persuasive and the initiatives of the European Union and the Organization for Economic Cooperation and Development and, in the US, the Fair Access to Science and Technology Research Act of 2015 (FASTR) will hopefully promote global access to peer-reviewed research findings. OA is critical for all scientists, but the financial costs are particularly problematic for those working in countries where resources are limited. These limitations of access have resulted in the emergence of the pirate research site *Sci-Hub*, established in 2011 by the Kazahstan-based scientist, Elbakyan, that has a

repository of greater than 46 million papers with free access [Schiermeir, 2015; Bohannon, 2016]. Elbakyan has stated: *"Journal paywalls are an example of something that works in the reverse direction,"* she says, *"making communication less open and efficient."* McNutt, Editor in Chief for Science and related publications stated: *"Journals have real costs, even though they don't pay authors or reviewers, as they help ensure accuracy, consistency, and clarity in scientific communication. For most of the Science journals, editors are paid professionals who carefully curate the journal content to bring readers an important and exciting array of discoveries"* [McNutt, 2016]. So, the question is: *"Is Sci-Hub altruism or copyright theft?"*

Open Access: Is the Answer That Simple?

A sting operation operated by *Science* in 2013 [Bohannon, 2013] suggests that all is not well with peer review at least as operated by some OA journals. The bait for the sting was a manuscript (multiple manuscripts to different journals, but with the same nonsensical central theme) focusing on the putative anti-cancer efficacy of a lichen-derived molecule, but with major flaws concerning the lack of a control (for the solvent, ethanol) so that any competent reviewer should easily reach a verdict of "reject". The outcome was that 157 journals accepted the manuscript and 98 responded with a rejection. Beall has offered this caution: *"Finally, advocates of open-access publication must stop pretending that the author-pays model is free of serious, long-term structural problems. Just because it works well in a few cases doesn't mean it always works"* [Beall, 2012].

Nonetheless, there are certainly highly positive features of the OA approach that can be developed. For instance, the Wellcome Open Research initiative for Wellcome grantees, launched in July 2016, uses a post-publication peer-review process to eliminate the potentially long publication delays noted above. Thus, submissions will be published immediately and followed by an open and transparent peer-review process wherein referees' reports and names will be published together with the paper [Wellcome Open Research, 2016]. This is an encouraging move that hopefully will be adopted by all open access journals as for OA to be truly open maintaining reviewer anonymity would be an oxy-moron.

Too Many Journals?

The increasing number of new journals raises the question about the quality of the published science. *"Soon more journals than authors?"* is the provocative title of an editorial in the journal *Acta Physiologica* and concerns the frequent email invitations that academics receive to write an article for an obscure journal [Persson, 2016]. Sometimes, the name of the journal may resemble that of an established and reputable journal. In recent years the emergence of *"Predatory Journals* and *"Hijacked Journals"* has taken advantage of academics who see the need to publish or perish and/or are frustrated with the often very slow peer review process provided by established journals [Beall, 2015, 2016a,b; Wellcome Open Research, 2016]. Typically predatory publishers charge a publication fee, but provide minimal, if any, editorial and publishing services that are the norm for legitimate journals. Hijacked journals operate out of bogus websites falsely representing a legitimate journal with often a very similar if not identical name as the legitimate journal for the purpose of fraudulently offering academics the opportunity to rapidly publish their research online for a fee. Beall, a Librarian at the University of Colorado Denver, first offered the term *"predatory open access"* in 2011 and has maintained a list of predatory journals that has risen from 18 in 2011 to 923 in 2016 [Beall, 2012, 2015, 2016a,b]. As Shen and Bjork [2015] have stated: *"These so-called predatory publishers are causing unfounded negative publicity for open access publishing general"*. In their 2015 study Shen and Bjork [2015] reported that in 2014 alone predatory journals published an estimated 420,000 articles in 8,000 active journals.

Clearly there needs to be a global response to predatory and hijacked journals; however, what should this be? Publications appearing in such journals potentially threaten the credibility of science so perhaps, as inferred by Beall, should citing such publications in, for instance, PubMed listed journal articles be prohibited [Beall, 2016c]? Academics who have published in such journals in order to boost their CV for promotion have seen their career advancement rolled back [Tin et al., 2014].

What Is the Value of the Journal Impact Factor (JIF)?

Charles Jennings, former editor with Nature and founder of Nature Neuroscience, stated: "To succeed in science; one must climb this pyramid: in academia at least; publication in one or more prestigious journals is the key to professional advancement"[Jennings, 2006]. Publishing one's scholarly works in the appropriate journal(s) (i.e. those listed in Thomson Reuters/ Institute for Scientific Information-ISI and covered by the Journal Citation Report) is obviously the best advice that can be given to a junior colleague and

arguably a strong deterrent to submitting to a predatory or hijacked journal; however, as discussed later this is not necessarily an easy path to follow. Unfortunately, there is a widespread misuse of the JIF particularly when used inappropriately for the consideration of matters of promotion, tenure and research grant evaluation with the not infrequent dismissive and sardonic use of the phrase: "he/she does not publish in high impact journals" – a problem that perhaps can be linked to anonymity in the peer review process. Would a referee make such an ambiguous comment if their name were to be identified? The exaggerated value of JIF as a biometric for assessing the impact of an individual publication, or scholar, is a problem that is only now beginning to be addressed. It is therefore important to remember that Eugene Garfield, founder of the Institute for Scientific Information, originally proposed the use of journal impact in 1955 as an aid to guide libraries as to how to manage their subscriptions and NOT for the purpose of judging the quality of individual publications [Garfield, 1955]. The JIF, as defined by Garfield, is derived from dividing the total number of citations of all of the articles for that journal published in the previous 2 years by the total number of articles published in the same 2 year period [Garfield, 2006]. The impact factor, IF, of a journal was not such a serious consideration for scientists in the 1960s or 1970s, but in the last 40 years has become the most important metric for academic appointments, promotions and tenure and for research funding.

In 1997, Seglen concluded that the IF of journals should not be used for evaluating research and as one of the summary points stated: *"Use of journal impact factors conceals the difference in article citation rates as articles in the most cited half of articles in a journal are cited 10 times as often as the least cited half"* [Seglen, 1997]. Furthermore, Seglen dismissed the dogma that publication in a high impact journal will enhance the impact of an article—thus it is the citation rates of the articles that determine the IF of a journal and not vice versa [Seglen, 1997] The inherent problems with the use of JIF to judge the quality of the scientific impact of an individual published paper are well documented [Triggle and Triggle, 2007; Chandrashekhar and Narula, 2015; Triggle, 2015]. The Wellcome Trust and The Higher Education Funding Council for England have made the argument that JIF should not be used for the evaluation of funding, appointments and promotion decisions [Gibney, 2013]. Other granting councils and organizations are adopting the same approach including the Australian Research Council, Canadian Institutes of Health Research and European Molecular Biology Organization (EMBO) as well as Research Councils UK [Larivière et al., 2016]. Although the tide is turning the JIF is still commonly used and, in fact, as a biometric it is seemingly, perhaps unwittingly, preferred by some scientists [Verma, 2015; Abbott et al., 2010; Callaway, 2016].

Alternative approaches to the use of IF to evaluate the impact of a scientist include the use of the "h-index" or *Hirsch index* that was introduced by the physicist, Jorge Hirsch as a measure of the impact of a scientist in the published literature in his/her field [Hirsch, 2005]. *"h"* equates the number of papers published that have been cited in other papers at least h times; in other words an "h-index" of 46 means that the individual has published 46 papers each of which has been cited at least 46 times. However, the "h-index" is most likely to favour the established investigator and be less favourable to the young scientist. The Office of Portfolio Analysis at the NIH has recently proposed the *Relative Citation Ratio*, RCR that arguably addresses these issues; however, it has yet to be vigorously used [Hutchins et al., 2015, 2016]. Perhaps a better, or at least an additional approach, is the use of *"citation distributions"* as proposed by Larivière et al. [2016] who evaluated the distribution of citations for 11 journals (*eLife, EMBO Journal, Journal of Informetrics, Nature, Nature Communications, PLOS Biology, PLOS Genetics, PLOS ONE, Proceedings of the Royal Society B: Biology Sciences, Science* and *Scientific Reports*). As might be predicted, they found that the distribution of citations is highly skewed to the left with 65-75% of the articles having fewer citations than would be predicted based on the JIF. Furthermore, long rightward tails also characterized these distributions such that 15-25% of the articles account for 50% of the citations. On the basis of their findings Larivière et al. have made the following recommendations [Larivière et al. 2016]:

1. *"We encourage journal editors and publishers that advertise or display JIFs to publish their own distributions using the above method, ideally alongside statements of support for the view that JIFs have little value in the assessment of individuals or individual pieces of work (see this example at the Royal Society, [Citation Metrics*, 2015*] Large publishers should be able to do this through subscriptions to Web of Science™ or Scopus™; smaller publishers may be able to ask their academic editors to generate the distributions for their journals."*
2. *"We encourage publishers to make their citation lists open via Crossref, so that citation data can be scrutinized and analyzed openly."*

3. *"We encourage all researchers to get an ORCID_iD, a digital identifier that provides unambiguous links to published papers and facilitates the consideration of a broader range of outputs in research assessment."*

It will be interesting to see whether the high impact journals adopt recommendations 1 and 2. Nature has recently indicated that will be providing extra metrics for assessing impact [Nature Editorial, 2016] and commenting on the Larivière *et al* paper of 2016 paper noted that for both Nature and Science approximately 75% of their articles failed to be cited at the level expected of their IF: that for Nature is currently 38.1. A similar argument is made by the current editor of Science [Berg, 2016]. Of particular interest is that on their website on July 11th 2016 the American Society of Microbiology (ASM) made the following announcement: *"The editors-in-chief of ASM journals and ASM leadership have decided to no longer advertise the impact factors of ASM journals on the journals' websites. This decision was made in order to avoid contributing to a distorted value system that inappropriately emphasizes high IFs. High-IF journals limit the number of accepted articles to create a perception of exclusivity, and individuals receive disproportionate rewards for articles in high IF journals, while science as a whole suffers from a distorted values system and delayed communication of research"* [ASM, 2016]. Perhaps the tide is now turning and impact rather than impact factor will be the primary metric for assessment?

So, Are the High Impact Prestigious Peer-Reviewed Journals Really That Influential?

Apparently not according to another study at the University of Montreal's School of Library and Information Sciences [Lozano et al., 2012]: these workers reported a significant drop based on a comparison of citations received over a 2-year period for in 1990 versus 2009. In 1990, approximately 50% of the top 5% of manuscripts appeared in the top 5% highest impact factor journals: however, by 2009 it was 36%. In conclusion, the most-cited articles are now more frequently published in lower impact journals [Lozano et al., 2012].

Schekman's View

Randy Schekman, a 2013 Nobel Prize recipient in Medicine for his contributions to cell communication, has lashed out at the prestige journals, Cell, Nature and Science calling them *"luxury journals"* referring to the IF as a gimmick and comparing the journals to fashion designers who create limited-edition handbags or suits [Schekman, 2013]. He goes further and recommends that: *"science must break the tyranny of the luxury journals."* As Schekman is editor-in-chief of *eLife* – a peer-reviewed OA journal for the biomedical and life sciences, launched at the end of 2012, perhaps his comments needs to be placed in appropriate context?

Peer Review—the Gatekeeper of Good Science?

Tantin makes an interesting analogy between peer review and baseball with the pitcher stopping the batter, the first baseman stopping the runner, etc. [Tantin, 2016]. In the publishing field the top journals employ professional editors whose sole job is often perceived to be preventing the majority of submissions ever reaching a scientific reviewer. Success with one of these elite journals thus represents a home run and a potential career advance. As Tantin points out the batting cage provides no obstacles to the batter and thus allows the batter to hit the ball as far as they can – an analogy to loading a preprint to an appropriate website.

The history of peer review has been well documented and will not be repeated here [Spier, 2002; Csiszar, 2016]. We also have previously commented on the important role that peer review plays as *"the gatekeeper"* for good science, but at the same time we and others have also pointed out many both perceived and real problems with the peer review process [Triggle and Triggle, 2007; Triggle, 2015]. Concerns with the transparency of peer review provide an attraction to easier routes for publishing one's research findings, particularly when careers are at stake. An often-stated concern is the increasing long period it takes to publish biomedical data. This was highlighted in a 2013 article in PNAS that noted that the lag time between submission and acceptance of a manuscript is often more than a year [Snyder, 2013]. Furthermore, the additional work often required by the reviewers arguably adds little to the scientific value of the paper and, in fact, serves only to delay access of potentially valuable data by the scientific community. In contrast 40 years ago publication of scientific manuscripts was faster and revisions comparatively minimal. Why has this changed? Snyder argues that the rapid advances in molecular biology are part of the problem prompting reviewers to request an exhaustive list of additional experiments that although possibly practical may take many months, or longer, to complete.

In an article appropriately entitled *"The Waiting Game"*, Powell discusses examples of the frustrations of long delays in publishing [Powell, 2016]. Powell cites one case of journal "shopping" that after an initial submission to Science finally, after 23 months, gets accepted in PLoS ONE, but only after three revisions. The questions to be asked of the referees and the journal editor is: "Are all of these requested revisions really essential?" "In requesting such changes are you merely delaying the publication and therefore access to data that would benefit other scientists?" Leaving aside the specifics of this particular case would it not be better for the editor to assert their ultimate authority and better referee the referees? Clarity is often needed as to which additional experiment(s) are really "acceptable" and absolutely essential to unambiguously clarify and support the conclusions versus those that are clearly in the category of "nice to have" and would be best suited for follow up manuscripts. Streamlining the publication of manuscripts as well as including the relevant critical comments from the referee(s) would not only benefit the authors and those reading the paper, but also enhance scientific progress. Such a process not only allows for earlier publication, but also, of course, earlier access to the data by other scientists. Scientific progress is thus enhanced and not repressed. Seeking the ultimate "mechanistic" answer, which often seems to be the argument from the anonymous reviewer, may sound appropriate to the reviewer and the editors, but science usually advances in small steps and what is mechanistic today will likely be considered descriptive tomorrow [Casadevall and Fang, 2009]. Long delays in publishing deny access of the data to other scientists and therefore may well result in unnecessary duplication of such protocols by other scientists. As we have previously discussed the difficulty in getting negative data published is another factor that may contribute to unnecessary duplication of effort, wasted research funds and delays in the advancement of knowledge [Triggle and Triggle, 2007; Triggle, 2015]. Snyder [2013] suggests that: *"Journals can change their modus operandi"* and journals *"should provide expeditious reviewing and reasonable requests for revision. Their cadre of reviewers should be trained in this modified approach"*.

The Fight against the Zombie Literature—Are Preprints the Answer?

The mainstream media routinely provides extensive coverage to incidents of scientific fraud and with good reason. The fraudulent association between the mumps, measles and rubella (MMR) vaccine and autism in children that was published in 1998 in *Lancet* [Wakefield et al, 1998] was finally withdrawn but not until 2010 [Editors of the Lancet, 2010]. This is just one example and the results of such fraud not only damage the reputation of all scientists, but also result in real harm to the global population due to a grass roots anti-vaccination movement that resulted in a reduction in MMR vaccine use, from a level of 92% in 1995 to 84% or less in 2002 that reduced herd immunity to a level below the 90-95% required to protect the entire population. In 1998, the year in which the original autism-association article was published, 56 measles cases were reported in the UK. By 2008, measles had become endemic in England and Wales with 1,348 cases and 2 confirmed deaths (Thomas, 2010). The Wakefield paper is an example, as pointed out by Spier [2009], of why using citations as a biometric may not necessarily reflect a positive impact on the discipline; yes, high interest, but for the wrong reasons. However, deliberate fraud and data manipulation is not the only issue and a likely larger problem is simply unintended error. In the biomedical field there are concerns about the use of questionable cell lines, specificity of antibodies, contaminated DNA, inappropriate protocol design and statistical analysis and even errors introduced at the publication stage that are not recognised by proof reading—in other words mistakes [Jarvis and Williams, 2016]. The problem is that such papers remain uncorrected in the scientific literature, may become highly cited and give rise to 2^{nd}, 3^{rd}, 4^{th} *ad infinitum* generations of potentially flawed data – what has been termed the "zombie literature" [Grant, 2016]. An example is the widespread use of mice as a model for studying human disease. Unlike humans and for that matter rats, mice are highly susceptible to torpor and subjecting them to, as is often the case for studies related to metabolism and to mimic human studies, prolonged periods (greater than 6h) of "overnight" fasting, particularly during their night (dark) cycle when mice are most active and food intake is high, results in a catabolic state with significant metabolic changes, a 10°C drop in core body temperature as well as resultant physiological changes, for instance a dramatic drop in heart rate, that may nullify the relevance of the results to the human condition [Webb et al., 1982; Ayala et al., 2006, 2010; Swoap and Gutilla, 2009]. Despite the recommendations of the NIH Mouse Metabolic Phenotyping Center Consortium [Ayala et al., 2010] the practice persists and the pile of zombie literature increases. Ioannidis raised the problem concerning reproducibility of data under the provocative title

"Why Most Published Research Findings Are False" [Ioannadis, 2005] identifying bias issues and the need for better statistical analysis, appropriate power analysis and larger sample sizes. One corollary discussed by Ioannidis is: *"The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true"* [Ioannidis, 2005]. Clearly the problem of reproducibility of data is now recognized as a serious issue that needs to be addressed [Ioannidis, 2005; Collins and Tabak, 2014; Begley and Ioannidis, 2015; Freedman et al., 2015; Jarvis and Williams, 2016]. It has been estimated that the cumulative direct cost of the failure in reproducibility of preclinical research results in the wastage of approximately US$28B/year, or 50% of all preclinical research, with much of the cost borne by those parties involved in attempting to translate preclinical discoveries to direct therapeutic benefits [Freedman et al., 2015].

In 2016 Berg et al. published an article entitled: *"Preprints for the life sciences—The time is right for biologists to post their research findings onto preprint servers"* [Berg et al., 2016]. A preprint represents a complete scientific manuscript that the authors upload, without charge, to a public server, usually before traditional peer review, thus allowing public access and potential feedback and improvement in the original manuscript. The idea, whilst new for the biological/medical sciences is not new for physics, mathematics, and computer sciences where it has been in use for over 20 years. A number of journals do already offer the possibility of posting preprints. For instance, EMBO states: *"EMBO Press encourages the posting of manuscripts before or coincidental with submission to a journal on a recognized preprint server. Most journals, including these, do not consider preprints to undermine novelty (see above). We recently implemented a 'one click' submission mechanism from bioRxiv to all EMBO Press publications."*"*[*http://www.embl.de/training/events/stayinformed/newsletter/*2016*/march/EMBOPress/*}*][EMBL, 2016]. However, as discussed by Berg *et al* it is not clear as to whether all publishing houses and scientific journals will accept manuscripts after they have been posted on a public server and how granting agencies will accept/encourage preprints in their evaluation of applications. However, the American Chemical Society, a very large publisher of society journals, has announced the launch of a preprint server for its journals [Widener, 2016].

Brian Nosek, the Executive Director and cofounder of the Center for Open Science (COS), promotes the concept: *"Creating single, open set of data to include all research events"* [Center for Open Science, 2016) with the goal of including all publications, grants, clinical trials, retractions etc. Thus, a manuscript would continue to evolve on line. The European correlate is the OpenAIRE project [OpenAIRE). The *Chronicle of Higher Education* selected Nosek as one of ten *"influencers"* who *"shook up higher education in the classroom, on campus, and beyond"* [Bartlett, 2015]. The impact of the preprint approach to the rapid global sharing of data remains to be seen; however, the potential positive impact on transparency and reproducibility is obvious as was emphasized by an article in *The Atlantic* by Yong [2015] concerning the reproducibility of psychological research. However, the interpretation of the statistical analysis cited by Yong originally published by the OSC has been questioned [Open Science Collaboration, 2015; Baker, 2016; Gilbert et al., 2016] and, if the rebuttal is correct, the reproducibility is better than stated, approximately 40%, and, in fact, closer to 70%. In rebutting the Gilbert et al., rebuttal, the OSC [Anderson et al., 2016] noted that the "very optimistic assessment is limited by statistical misconceptions and by causal inferences from selectively interpreted, correlational data. Using the Reproducibility Project: Psychology data, both optimistic and pessimistic conclusions about reproducibility are possible, and neither are yet warranted."

Rent Seeking: From Publishing to Medicine

In 1941, Roosevelt noted that: "The third is freedom from want, which translated into world terms, means economic understandings which will ensure to every nation a **healthy** peacetime life for its inhabitants – everywhere in the world" [Emphasis added] [Roosevelt, 1941].

The continuing progress made in providing OA to the scientific literature has been driven, as discussed previously, by a variety of factors including the increasing recognition that basic science, largely funded by public funds, should be freely available to all according to Merton's ethos of science [Merton, 1942a; Garfield, 1996b; Chandrashekhar and Narula, 2015; Triggle, 2015]. This represents a transition from the current monopolistic rent-seeking practices of commercial publishing.

However, this success, albeit only partial, still leaves open the question of the access to and availability of the fruits of open science. Nowhere is this more important than in the broad area of health. Paradoxically perhaps, the US, despite its wealth and the lofty rhetoric of Roosevelt, continues to lags conspicuously behind the rest of the developed world in health outcomes of its citizens [US National Academy

TABLE 1. USA World Health Comparisons

Life expectancy	Infant mortality	Maternal mortality	Childhood poverty	Teenage pregnancy
43/224*	58/224†	46/184‡	2/34¶	1/28§

*The US is exceptional among OECD countries with life expectancy actually decreasing for low educated whites ranking 43rd out of 224 countries for life expectancy [Sasson, 2016].
†The USA ranks 58th of 224 for infant mortality with 5.83 deaths per 1000 live births compared to the lowest, Monaco, with 1.82 [Central Intelligence Agency Factbook, 2015].
‡Maternal mortality rates have actually increased in the US by 26.6% from 2000-2014 [World health Organization, 2015]. This rise is particularly dramatic in Texas where the rate doubled between 2010 and 2014 [Phillips, 2016]. Overall the USA ranks 46th out of 184 for maternal mortality.
¶34th of 35 nations for childhood poverty with 23.1% of children living in households with equivalent income lower than 50% of national median [Adamson, 2012]
§highest of 28 for teenage pregnancy [health > teenage pregnancy, 1998; Sedgh et al., 2015].

of Sciences, 2013; Table 1], and has extraordinary levels of debt and bankruptcy attributable to unaffordable medical costs exacerbated by, perhaps surprising to some, very high poverty levels in the US population [Gutierrez, 2016; McElwee, 2016].

If, as Roosevelt's speech indicates, we should regard the health of a nation's citizens as a public good then what impact does restricted access to the basic information of scientific publications and knowledge intended to enhance this public good have on the mechanisms of the delivery of medical care in an economy society largely dominated by free market principles?

Accordingly the following issues will likely dominate thinking concerning the delivery of medical care over the next several decades:

1. The role of economic markets in delivering health care
2. Antibiotic resistance, the impact of climate change and the spread of new diseases.
3. The availability and use of genetic knowledge

The economic term *"rent seeking"* defines the behaviour of individuals or organizations that generates economic benefits via political and monopolistic practices above the true economic worth of the physical or intellectual commodity. These additional costs are borne by the community at large and contribute to social inequality and tension [Tullock 1967; Krueger, 1974; Deaton, 2013]. Thus the oligopoly of scientific publishing [Larivière et al., 2015] may be characterized as a form of rent seeking, although the advent of open scientific publishing is now in the process of changing this model.

In the broader context of healthcare in the US, the increasing consolidation of health insurance companies and hospitals has led to a marked decrease in competition that is paralleled by escalating health care costs [Hervey et al., 2015; Cooper, 2016; Xu et al., 2016]. The recent decision by the insurance company, Aetna to exit the individual insurance market in the US that is mandated by the Affordable Care Act (aka Obamacare) because it was refused permission by the Department of Justice to merge with Humana will leave many states with little or no competition in that aspect of the health insurance market [Tracer et al., 2015; Dayen, 2016], a not unexpected outcome given the broad remit of the ACA to provide health care to the previously uninsured who are in greater need of health care services [Turner, 2016], without mandating the necessary universal coverage to ensure that both healthy and sick individuals are covered.

The pharmaceutical industry continued to undergo significant consolidation; the largest number ever of acquisitions and mergers in the industry occurred in 2015 [de la Merced et al., 2015; Ward, 2015a]. Thus, Pfizer's abortive bids to merge with first AstraZeneca and then Allergan were perceived as largely due to its desire to reduce its corporate tax rate and to minimize the tax on its unrepatriated offshore dollars [Ward, 2015b; Pfeffer, 2016]. Such mergers tend to permit price increases and also to decrease research and development investment [LaMattina, 2011; Lo, 2015; de la Merced et al., 2015].

According to Teles [2015] and Furman and Orszag [2015] rent seeking is a significant contributor to the upward redistribution of wealth and the increasing inequality seen in the US and many other countries. Even *The Economist* has argued that U.S. profits are too high across the board because of inadequate competition [The Economist, 2016]. This increasing inequality has profound effects on health outcomes with a significant relationship between adult longevity and infant mortality (as well as

educational status) and has been comprehensively summarized by Marmot in the book, *The Health Gap* [Marmot, 2015].

Rent seeking can be facilitated by many factors, notably the impact of federal and state regulatory practices including patents, copyright laws and extensions, professional licensing restrictions, financial conglomerates, trade agreements, trade unions and trade associations all of which function primarily in their own interest, albeit with a claim to the overall public interest. At the corporate level, Friedman famously stated that, *"The only social responsibility of business is to increase its profits"* [Friedman, 1970]: perhaps a bridge too far [Healy et al., 2015]. As described by the economist, Olson the competitive and political advantage exerted by these special interest groups is highly detrimental to the well being of the nation state [Olson, 1982]. Furthermore, it is likely that, if signed and implemented, the Trans-Pacific-Partnership (TPP) trade agreement, which despite its politically claimed great public benefits, has been conducted without any public input, will only increase monopolistic practices in healthcare, drug and medicines pricing and availability via a variety of patent and exclusivity extensions [Kilie et al., 2015; Public Citizen, 2015]. The delivery of medical care to the patient is also subject to rent seeking for a number of reasons. In the terms outlined by the economist, Arrow [1963], the economics of medical care do not follow a normative economic model based on competitive principles for several reasons:

1. The need for medical care is both irregular and unpredictable. In crude terms a patient in need of an antibiotic, an ambulance, cardiac or other emergency care is unable to postpone costs in the hope of a cheaper alternative at some future date or time.
2. There is an asymmetry of knowledge between the recipient of care and the provider of such care. The patient is rarely in a position to challenge or to negotiate with medical authority.
3. There is uncertainty as to the outcome of medical care. Recovery from disease is neither always certain or predictable. And there is almost, without exception, no opportunity to "test" a procedure beforehand.
4. Restriction of supply of medical care. The availability of care is restricted by a variety of practices, including licensing of medical personnel (guild restrictions), monopolistic patents on medical products and procedures and restrictions on access to medical care services by insurance protocols and decisions.

Accordingly, medicines delivery in a market-based economy is not seen as a *"public good"*, but rather as primarily a profit-making enterprise with the attendant limitations of access based primarily on profit considerations rather than public need and health priorities [Triggle, 2001, 2004].

A full discussion of these issues in terms of the delivery of medical care lies outside the scope of this Commentary and discussion will be confined to the problems of access to and delivery of pharmaceutical products. However, it must be noted that the considerations outlined by Arrow [1963] are not unique to the delivery of medical care. Asymmetry of information in financial decisions can lead to disastrous outcomes, even worldwide, as seen in the economic crash of 2008/2009 [Reinhardt, 2010].

Monopolistic Practices in Access to Pharmaceutical Products

Rent seeking in the delivery of medicines became dramatically apparent to the public in 2015 when the founder and CEO of Turing Pharmaceuticals, acquired the rights to the generic anti-parasitic drug Daraprim (pyrimethamine) and immediately raised the price from $13.50 a tablet to $750 a tablet – a 55-fold price increase [Pollack, 2015]. Daraprim is available for 7 cents a tablet in India and less than $1.00 a tablet in the UK. This is, however, but one example of dramatic rent seeking price increases in the generic drug market. Valeant Pharmaceuticals similarly raised the prices of two generic cardiac drugs, Nitropress (nitroprusside) and Isuprel (isoproterenol) by similar amounts [Morgensen, 2015]. With no apparent sense of irony, a Valeant executive, argued to a Congressional Committee that, *"Because these drugs are hospital administered and not purchased by patients directly, increasing the costs of the drugs to hospitals would affect the hospital's profits on these procedures, but it should not reduce patient access"* [Pollackand Huetteman, 2016]. This remarkable comment finds its parallel in an old fable of now unknown origin:

> *An old farmer was driving to market with his horse and cart to sell his produce and saw his neighbour walking to market and bowed down with a heavy sack of produce. He offered him a ride that the old farmer accepted gratefully. However, after about a mile the farmer saw that his neighbour was still burdened by the heavy sack upon his shoulders and suggested that he place his sack upon the floor of the cart. The neighbour*

refused stating that, "He did not wish to place the burden of his weighty sack upon the horse"!

Many similar examples of dramatic increases in generic dug prices are available [Hoffman, 2016]. Perhaps, most notably the price of the anti-tuberculosis drug cycloserine went from $500 for 30 tablets to $10,800 after its acquisition by Rodelis Therapeutics. Similarly, the cost of the EpiPen, a vital medication device for allergic emergencies and containing a miniscule amount (worth about $1) of the off patent epinephrine, has increased in cost some 400% since Mylan purchased the device from Merck KGaA [Koons and Langreth, 2015] and subsequently completed a corporate inversion to a lower corporate tax entity, The Netherlands [Edney and House, 2016]. However, many of the drugs discussed have limited markets and although the cost increases are significant to the individual patient/insurance companies other factors likely dominate the escalating costs of U.S. health care. Per capita prescription drug spending in the US is the highest in the world and prices on existing prescription drugs regularly rise at levels of between 10-20%, far above inflation and where it can be assumed that the research and development costs of these drugs have been fully recovered [Friedman and Weiner, 2016; Staton, 2014; Langreth and Spalding, 2016; Rocco et al., 2016]. A further highly relevant example is the dramatic price increases for the various forms of the generic anti-opioid drug, naloxone with increase of 10-20 fold over the past several years [Helfond, 2016; Karlin-Smith, 2016]. Since deaths from opioid overdose now constitute a public health emergency in the US these price increases represent a lethal example of market failure.

A related area of concern to medicines availability is the very high prices charged for newly introduced entities that may offer significant advances in health benefit. Notable examples include new anti-cancer drugs and so-called orphan drugs where significant concerns over pricing, availability and cost effectiveness have been repeatedly expressed [Kantarjian et al., 2014; Howard et al., 2015; Bach, 2016; Kocher and Roberts, 2016]. Thus, Howard *et al* [2015] comment that:" *if insurers restricted coverage to drugs that improved survival time by an economically significant amount, perhaps there would be more of them*". However, it has also been argued with some cogency that high economic returns are necessary to ensure continuing innovation in the pharmaceutical industry [Berndt et al., 2015]. Whether this is really true is debatable; Kessel has suggested that the industry needs to focus less on its bottom line and more on long-term investment [Kessel, 2011]. Additionally, the argument may simply reflect the fact that much of the low-hanging fruit on the pharmaceutical tree has already been picked.

A specific example is the anti-Hepatitis C (HCV) drug, Sovaldi (sofosbuvir), a viral RNA polymerase inhibitor, marketed by Gilead Sciences at a cost of $84,000 for a 12 week treatment regimen with profit of $12.1 billion from total sales of $24.9 billion in 2014 [Ollendorf et al., 2014; Nichols, 2015]. The initial purchase price of $11 billion when Gilead acquired Pharmasett, Inc in 2012 [Langreth, 2015] has thus yielded a generous return for the company with a report from the US Senate Finance Committee stating that the pricing strategy was driven primarily by revenue considerations [Wyden and Wyden-Grassley, 2015] with generous compensation for the CEO of the company [Staton, 2015; Sachs, 2016]. Whether justifiable or not such CEO compensation has increased dramatically in recent years across a broad range of industries having grown 90 times faster than average worker compensation [Mishel and Davis, 2015]. Such changes contribute to the increasing social tensions in progressively unequal societies [Krueger, 1974; Olson, 1982; Deaton, 2013; Furman and Orszag, 2015; Teles, 2015].

However, Sovaldi even at its current cost is certainly more effective than earlier treatments, which cost more and had a significantly lower cure rate [LaMattina, 2014; Gilman and Dowden, 2016]. Thus the three drug combination of telaprevir, peginterferon and ribavirin had a cure rate of 44%, cost approximately $190,000 per patient and had poor patient compliance [LaMattina, 2014; Smith, 2014]. Nonetheless, given that HCV, an asymptomatic disease, affects approximately 2.7 million individuals in the US and some 185 million worldwide, a price of $84,000 per patient is clearly not economically feasible even if society prices the value of a human life at $84,000. Insurance companies have described the $84,000 price as *"a blank check.[that].will blow up employer benefit costs… and wreak havoc on the federal debt"* [LaMattina, 2014]. The same rent seeking logic would of course lead to the conclusion that a weeks' life-saving treatment of pneumonia with a generic antibiotic or rehydration in a cholera patient is also worth $84,000! [Blumenthal, 2016]. The reaction to the cost of Solvadi and similar drugs, despite their effectiveness, raises major issues in the provision of health care as noted previously by Triggle and Williams [2015]. Public expectations often run counter to economic realities and discussions of cost-benefit data appear unseemly when life and death decisions in health care are being made. Ultimately,

the decisions made for the provision of health care will depend on whether health care is regarded as a "public good" or as commercial market, on what level of expenditure is deemed acceptable, how that expenditure will be provided and how will the allocation of health expenditures be made.

However, regardless of such arguments and whatever entity is paying the cost—patient, government or insurance company—the cost is ultimately borne by the public and this will ultimately raise the issue of pricing controls, controls, restraints on use and even the intrusion of eminent domain purchasing of pharmaceutical patents [Bach, 2016]. The nonprofit organization, Drugs for Neglected Diseases Initiative (DNDI) established with the aim of bypassing the expensive commercial route for drug development apparently by being more efficient, was reported as markedly reducing costs as compared to pharma. DNDI spent $262 million over 10 years to produce 5 drugs/drug combinations while the pharmaceutical industry spends an average of $2.6 billion to produce one drug [CEPR, 2015] and will soon seek approval for a new drug for sleeping sickness [Maxmen, 2016]. The contribution of efficiency to the DNDI costs for drug development has been challenged [Lowe, 2015] as all of the drugs this organization has developed were repurposed or reformulated generic drug entities, Of additional interest is a recent study documenting the role of twenty-six transformative drugs that were approved between 1984 and 2009, many of which were based on academic research supported by federal funding [Kesselheim et al., 2015]. This of course is exactly the role for government support of basic science advocated by in a seminal report by Bush [1945]. These and related issues raise critical questions worldwide of how to pay for the increasing demands of health care raised by an expanding global population in the context of increasing medical advances.

Antibiotic resistance, neglected diseases and the impact of climate change and the spread of new diseases

Society faces three major and global public health threats. First, the rapidly developing threat of microbial resistance to antibiotics. [O'Neill, 2014]. With the discovery of *E. coli* resistant to the antibiotic colistin first in China and now in the US, the threat has evolved into a crisis [Levy and Breithaupt, 2014; Lusniak, 2014; McGann et al., 2016; Rosen, 2016]. There is thus an urgent and global need to revitalize the process of antibiotic innovation discovery [Outterson et al., 2015]. The announcement of CARB-X, a new public-private partnership to accelerate antibiotic discovery and development is thus very appropriate [Outterson et al., 2016]. Second, there continues to be very significant neglect in the development of new drugs for neglected diseases (including neglected tropical diseases) – malaria, tuberculosis, diarrheal disorders, sleeping sickness, Chagas, Ebola, Dengue fever, etc. [Centers for Disease Control]. For the 15-year period 1975-1999 only 1.1% of new therapeutic entities were developed for neglected diseases. Since then the outlook has improved somewhat, but is still inadequate: from 2000 −2011 4% of the 850 newly registered therapeutic products were for neglected diseases [Jones et al., 2008; Pedrique et al., 2013]. Finally, global warming and climate change are impacting the spread and location of tropical diseases such that Ebola, Dengue fever, malaria and most recently the West Nile and Zika viruses are now emerging in new locations [Lindgren et al., 2012; Wu et al., 2016]. In an opinion piece Hoberg and Brooks [2015] noted that: "*We exist at the nexus of cascading crises for biodiversity (species loss), accelerating climate warming, along with attendant ecological perturbation and emerging infectious diseases (EIDs)*". And in a commentary on the Hoberg and Brooks article -" *It's not that there's going to be one "Andromeda Strain" that will wipe everybody out on the planet-.There are going to be a lot of localized outbreaks putting pressure on medical and veterinary health systems. It will be the death of a thousand cuts*" [Science Daily, 2015]. These neglected diseases represent a very significant economic burden, particularly for the poorest people in the world with some seventeen neglected diseases representing the fourth largest disease burden of all communicable diseases [Norris et al., 2012].

Who Owns Biology?

As the 20th century may be said to belong to the great discoveries of physics in the 19th century—from steam engines to jet engines, to radio, television, computers and nuclear weapons—so the 21st century will belong to the great discoveries in biology in the 20th Century—notably molecular biology [Economist Leader, 2007]. Given the already proven promise of the application of molecular biology to medicine the critical practical and ethical issues to be confronted are who owns and who benefits from the fruits of these discoveries? [Triggle, 2004; Robinson et al., 2005]. The issues may be illustrated by these selected examples.

Oil-eating bacteria and the first gene patent In 1980, the U.S. Supreme Court ruled in the case of

Diamond vs. Chakrabarty that oil-eating bacteria created in the laboratory by genetic engineering were patentable [Katz, 2015]. This ruling opened the door for the patenting of human genes.

BRCA breast cancer diagnostics. In the *Association for Molecular Pathology et al. vs. Myriad Genetics* case, the court ruled unanimously that the BRCA breast cancer genes and most importantly, *"any naturally occurring"* genes are products of nature and, therefore, not patentable [Cook-Deegan and Nichaus, 2014]. Prior to the latter decision, Myriad had claimed rights on all diagnostic procedures based on BRCA1 and BRCA2 genes, procedures that cost upwards of $3000 per test: for many patients these tests were unavailable because of cost. Hence, the basic research underlying these discoveries did not become an open scientific benefit, but rather became an example of monopolistic rent seeking. However, in *Myriad* the Court did rule that cDNA is patentable because it is synthetic and it is synthesized DNA that is the basis for much molecular biology research and the creation of diagnostic tests. The full implications of the *Myriad* and related decisions remain to be determined as discussed in several reviews [Feldman, 2014; Lee, 2015; Stern, 2013]. The decision does, however, have the potential to further constrain patent development [Lee, 2015]. Additionally, the question arises as to whether the existing legal system has the ability to evaluate such complex issues of molecular biology. In the *Myriad* case, the late Justice Scalia commented, *"I join the judgement of the Court. . ..except the portions going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief"* [Pryes, 2013].

Furthermore, the Court's decision did not shed light on the question of the ownership of the genetic information obtained in such testing procedures. Myriad Genetics is currently embroiled in a lawsuit over exactly this issue, having refused to release this information to patients [Hayden, 2016]. This is, however, simply an example of a much larger problem. As genetic databases proliferate what mechanisms are in place to ensure both privacy AND that the data are seen as a public good? Heller and Eisenberg have questioned whether patents can deter innovation by creating a scientific *"anti-commons"* in which resources are under-utilized because of legal constraints [Heller and Eisenberg, 1998; Eisenberg, 2008; Offord, 2016; Williams, 2010]. An Advisory Committee to the U.S. Secretary of Health and Human Services concluded in 2010 (prior to the Myriad decision) that, *"patent-derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and laboratory-developed tests*. [Secretary's Advisory Committee for Genetics, Health and Society, 2010] and noted that the commercial activity derived from human genes was greater in those genes in the public domain. However, of equal importance is the question of whether private ownership of genetic data hinders health care delivery. In a broader perspective Wilbanks and Topol [2016] have argued that the privatization of health data in general by technology companies may both widen health inequalities and diminish the use of such data in health research.

CONCLUSIONS

The 21st century will present major challenges – possibly existential challenges – to human existence. Climate change, population growth, energy, food, water and biodiversity will be under severe stress [The Oxford Martin School 2013; Oreskes and Conway, 2013; Turner, 2014]. To avoid *"Tragedy of the Commons"* scenarios [Hardin, 1968] will require global collaboration and coordination at social and scientific levels in a hitherto unparalleled manner. And simultaneously there must be recognition of the impact of scientific knowledge in areas such as artificial intelligence and gene editing that have the capacity to both physically and biologically transform the human race [Avent, 2013; Ashrafian, 2015; West, 2015; Boeke et al., 2016; Butler, 2016]. If we are to be successful in this endeavour then scientific knowledge must be recognized as a global public commons available to all [Dalrymple, 2003; Galston, 2013]. And we must recognize the urgent need to discuss critically and publicly the ethical issues that accompany the introduction of new and untested innovations [Jasanoff, 2016].

Currently, this is not the case. Both scientific knowledge through publishing and the applications of science in computing, financial industries, media, medicine etc., are dominated by monopolistic, rent seeking practices that simultaneously limit and overcharge for public access. Universities, those great engines for the creation and dissemination of fundamental knowledge have yielded too frequently to the temporary lure of scientific profit: the results damage both the concept of the university and science itself [Hilzik 2016; Pelikan, 1992; Triggle, 2004; Sherkow, 2016a].

In an interesting development the Montreal Neurological Institute and Hospital will require all of its research to be open without restrictions and, in contrast to many universities, will not pursue patents on its discoveries [Owens, 2016]. One argument for this radical change is that open science really will

speed up innovation. A second reason is that patents are not the automatic drivers of innovation as has been commonly assumed [Shulman, 1999; Feldman and Lemley, 2015; Grabowski et al., 2015; Wadha, 2015]; furthermore, universities frequently waste a lot of time and money patenting where the likelihood of any significant financial benefit is minimal [Owens, 2016]. A concern, as already addressed in this commentary, is the problem with the high failure rate to replicate pre-clinical research data and, as commented by the Chief Scientific Officer at Pfizer's Neuroscience and Pain Research Unit in Cambridge, Massachusetts: *"Universities tend to slather IP in every finding, regardless of its potential value"* [Owens, 2016]. This does not exclude all opportunities for patenting, but, as outlined by Owens, there are advantages to sharing in the early stages of research. The argument for holding on to your data until after you publish is also not a philosophy supported at the Allen Institute in Seattle, which has also followed an open science model [Owens, 2016]; whether this is a universally acceptable and workable model remains to be seen.

Given the challenges ahead, particularly in the interface between population growth, climate change and global public health, new approaches to open science are urgently needed [Edwards, 2016; Low et al., 2016; Owens, 2016].

However, considerable progress has been made, although not without problems such as the rise of "predatory journals" in the field of scientific publishing. Nonetheless, with the rise of several OA journals, the increasing use of preprint servers, the increasing recognition by commercial publishers of the need for wider science dissemination and government mandates requiring that all publicly funded science be OA are rapidly changing the scientific publishing landscape. It is highly probable that within the next decade open publishing will be the norm for science, with the possible exception of a few "flagship" prestige journals where the perceived value of editorial curation will still be recognized and rewarded.

In contrast, the need for transparent and open medicine and medicine delivery remains critical. Although significant positive steps have been taken to encourage open discovery in the areas of neglected and tropical diseases [Hodson, 2016], continuation of the current model of drug development based on rent-seeking, the development of extremely expensive drugs that treat limited numbers of patients and the avoidance of therapeutic areas where investment would not enhance shareholder value is neither economically nor morally sustainable [Lee, 2015]. Munos [2006] has made powerful arguments in favor of open-source research and development to stimulate drug research and there are now major public-private partnerships for drug and vaccine development in place: these include collaborations between drug companies, philanthropy-based financing, collaborations between industry and universities, the sharing of chemical databases and the development of common chemical and biological toolkits [Owens, 2016; Munos, 2006, 2016]. On-line sharing of data becomes particularly important with the rise of new infectious diseases such as Zika virus [McNeil, 2016]. Of particular importance is the area of antibiotic resistance where we need urgently both radically new approaches for discovery and development and simultaneously public health measures to slow the progression of drug resistance [Amabile-Cuevas, 2016]. Advances in many areas can be obtained through the use of shared processing power of personal computers and through the role of scientific games such as *Foldit* and *Planet Hunters* [Burke, 2011; Mohammadi, 2014].

However, despite the global urgency around these issues it is dispiriting in the extreme to view the current intellectual property disputes of new genomic techniques such as CRISPR-cas9 gene editing [Esvelt, 2016]. In principle, as Esvelt has argued, gene editing science could be a driving force for open science in one of the most exciting developments ever in biology. However, it has turned into a patent dispute between teams at the University of California and the Massachusetts Institute of Technology over who made the first discoveries and who owns the rights to this technology and presumably who will profit both in terms of royalty income and personal credit [Regaldo, 2016; Sherkow, 2016a,b; Valdivia, 2016]. Should, for example, restrictive or exclusive licenses be granted will academic science be restricted and will commercial firms engage in rent seeking for any therapeutic discoveries that may emerge? And what are the ethical implications for the use of this technology that has the potential for permanent human genome alteration? —Huxley's "*Brave New World*" or Atwood's *"Oryx and Crake"* [Atwood, 2003; Huxley, 1932]? Regardless of such strictures Hedge Fund managers and others awash with Silicon Valley money are working to extend human life, presumably their own, well into the 120s, regardless apparently of social consequences and the prospect of 120-year-old politicians running governments [Corbyn, 2015; Cheating Death, 2016].

Finally, the CRISPR-Cas9 issue brings to the forefront the very nature of science itself, scientific discovery and scientific patents. In a letter to Robert Hooke in February 1676, Newton wrote, *"If I have*

seen further it is by standing on the shoulders of giants" [Newton, 1675], and in more contemporary terms Merton wrote of the accumulated and shared scientific knowledge that underlies discovery [Merton, 1942a,b]. Given the multiple origins of scientific discoveries [Hsu et al., 2014; Regaldo, 2016; Zhang, 2016] and given the critical needs for scientific solutions to the challenges of the 21st Century, particularly in the area of global health it is necessary to ask again whether the current model of restrictive intellectual property protection via patent and copyright protection remains appropriate [Boldrin and Levine, 2010; Ledford, 2016]. The human right to science and its applications will be of critical significance to continuing human development in the challenging 21st century [Chapman and Wyndham, 2013]. Balancing this right against the expressed views of Adam Smith [Smith, 1776] remains a determining issue: "*People of the same trade or profession seldom meet together even for merriment and diversion, but the conversation ends in a conspiracy against the public or some contrivance to raise prices*".

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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