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EDITORIAL

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Publishing coronavirology: Peering into peer(less?) review

Back in April of this year, *The FASEB Journal* adopted a fast-track publication policy in which articles on the SARS-CoV-2 pandemic submitted to our Hypotheses, Perspectives or Review Article categories could, at the discretion of the handling editor, be accepted without further review. In taking this step, I realized that there was a degree of risk but felt that this global health crisis warranted it. Regular research articles are not eligible for this process.

The first of these fast-tracked items was, in a sense, my May editorial[1] in that although these are reviewed by a standing FASEB committee, always appreciated, the editorial was put through production very fast. The same issue carried the first three coronavirus papers accepted under the fast-track policy, of which one was in the Hypotheses category[2] and the other two were Review articles.[3,4] The June issue contained two more fast-tracked Review articles.[5,6] July contained one fast-tracked Hypothesis article,[7] and we have two more Hypotheses in the present issue.[8,9]

The point to be made here, or perhaps one could say admitted, is that in none of these cases[2-9] was the handling editor a "peer" with regard to the specific topic. Rather, an element of judgment was the sole factor. (Other submissions eligible for the fast-track process have instead undergone standard review, and these are currently in process; one submission so far was rejected without review). Our readership's response to the fast-tracked papers has been very lively, and one article in particular, on hydroxychloroquine and chloroquine,[4] generated considerable media attention, as it was one of the first comprehensive reviews on the experience with these drugs for COVID-19. Of course, it could have turned out (and may still) that one or more of these fast-tracked papers could set off a false lead and misdirect valuable research time and resources. It is, in my view, a risk worth taking. (And again, research articles are ineligible for this process.)

My reasons for reciting all this has arisen in the context of two controversial recent publications in the fast-moving SARS-CoV-2 field.[10,11] The first of these, published in *The New England Journal of Medicine* (*NEJM*) on May 1, claimed to have shown that the deployment of hypertension drugs such as angiotensin-converting enzyme (ACE) inhibitors did not elevate death rates of COVID-19 patients,[10] countering previous reports to the contrary. Subsequent to this article's publication, a large number of experts sent an open letter to the *NEJM* that conveyed their concerns about the database used (*vide infra*), leading the journal to post an Expression of Concern, asking the authors to verify that the data in the paper were reliable. The authors subsequently asked that the paper be retracted, stating that they had been unable to verify the data set used.

A second study, published in *The Lancet* on May 22, claimed to have shown that the antimalarial drugs hydroxychloroquine and chloroquine provided no benefit to COVID-19 patients and that indeed treated individuals had a higher incidence of an irregular heart rhythm and death.[11] In a letter to *The Lancet's* editor on May 28, 120 scientists called the study into question, resulting in the journal issuing of an Expression of Concern. The skepticism centered on the vast patient database employed in the study which the letter's signatories claimed was so comprehensive and meticulous as to the number of patients, demographic details, and dosing regimens as to defy belief. It included records from almost 15,000 patients treated with either drug (and with or without a concurrent antibiotic) and 81,000 nontreated control patients, at 671 hospitals on six continents. The *Lancet* study was observational, not a randomized, controlled clinical trial. Critics have pointed to additional issues, including the fact that the study did not disclose the clinical details, so that it remained possible that treated patients were sicker than the untreated ones. It was also pointed out that the study included 4402 patients in Africa, whereas an expert on healthcare facilities on the continent was quoted as doubting many African hospitals would have such detailed records.

Then, a third controversy arose around a preprint that had been put up on the Social Science Research Network server in April, authored by the some of the same investigators that published the *NEJM* and *Lancet* papers. It concluded that the antiparasitic drug ivermectin very substantially lowered the COVID-19 death rate. The lead author subsequently took down this preprint.

Beyond all dealing with COVID-19, these three studies had something in common. They all employed the same, above-mentioned patient database, compiled and owned by Surgisphere, a company in Chicago. The proper handling of the first two published studies by the respective journal

editors, further details of the controversy, and the responses of the various authors, as well as that of Surgisphere, have been described in recent accounts (*e.g.* 12-14), and these stories are still evolving as this editorial goes to press. Surgisphere refused to allow independent auditors to examine the data set, citing the provisions of their client contracts, as well as patient confidentiality. A major issue is the degree to which the two retracted papers and the posted preprint may have improperly influenced other trials or treatment regimens of these drugs for COVID-19. My commentary here has to do with the degree to which peer review was challenged by these papers.

The two published papers[10,11] went through peer review. In hindsight, it seems possible that some reviewers found the vast size of the patient cohorts to be an enabling element in accepting the conclusions. Calls have been made for the Editors-in-Chief of *The Lancet* and *NEJM* to release the reviews, but I am doubtful that will happen or would even be ideal. It also has to be said that, at the time these two papers were submitted, the value of the two antimalarial drugs and ACE inhibitors was unsettled. The reviewers of each manuscript were likely peers to the extent they were well aware of the need to get these two therapeutic issues resolved. But were they peers in the sense of an awareness of the Surgisphere database and, if so, its possible flaws? We do not know if any reviewers, of either paper, asked for more details about the database and, if so, whether such were provided. So, one can almost ponder that the review of the two papers could be considered, at least with respect to the database, "peerless," this term not pejorative to the reviewers but a speculation as the impossible position they were in.

A related issue is the degree to which study results should be announced prior to publication. Given the public health gravitas of SARS-CoV-2, it is only natural for investigators to want to do so. On June 16, a team at the University of Oxford announced that dexamethasone has very significant therapeutic value in treating patients with advanced COVID-19. Unlike the issues swirling around the antimalarial drugs and ACE inhibitors, and perhaps also around ivermectin, the notion that dexamethasone is ameliorative in the airways of advanced COVID-19 patients seems almost like a Rudyard Kipling “just-so” story. Everything we know about this steroid would suggest, or even predict, that it would be. We know the virus dismantles so much in the respiratory epithelium and other cell types present, and probably does yet more than we know, and yet, it would not be surprising that, in its palliative effect, dexamethasone might help just enough for some patients to rally, especially as there is recent evidence that the blood vessel endothelia around the air sacs are also hit by the virus. But, despite these physiological notions and statements of optimism from some commentators, others have, once again, cautioned that this study has not been subjected to peer review and been published.

So, it is my hope that these are ongoing lessons being learned, the present participle, just as is the word "science" itself descends from the Latin for "knowing" (*sciens*). There may unavoidably be some coronavirus manuscripts coming that are "peerless," and finding these studies to be seamless may be a challenge. But what encourages me are the ways in which the editors of the first two controversial papers handled the matter, which sets a standard (actually, one already in place at these two distinguished journals).

But, there is one more thing for which we can be grateful. Once these two papers were published, there *was* peer review, in that many who sensed flaws had the experience to do so, and they came forward to serve.

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