

# Bias in the research literature and conflict of interest: an issue for publishers, editors, reviewers and authors, and it is not just about the money

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Conflicts of interest (COIs) of researchers have been a frequent topic recently in the popular press and scientific journals. Of particular interest to psychiatric researchers are the investigations in the US senate, led by Senator Charles Grassley. A recent article in *Science* discusses the history and current state of these investigations.<sup>1</sup> For those who like to keep score, *Science* has a list of the 9 psychiatric researchers who have been investigated, the amounts of money they received from drug companies and the amounts they mention in COI disclosures.<sup>2</sup> Much of what has been written about COI concerns drug company payments to researchers. However, COIs are an issue for publishers and editors of journals, reviewers of manuscripts and authors. Conflicts of interest exist in every aspect of the production of research journals, and the conflicts derive from more than just money paid to researchers by drug companies. The purpose of this editorial is first to discuss the nature of COIs and to describe some of the human behavioural research relevant to COIs. I will then discuss how COIs pervade every aspect of publishing and how the *Journal of Psychiatry and Neuroscience* attempts to deal with these issues. Finally, I will argue that there is no entirely satisfactory way of dealing with COIs, but that all researchers should be aware of the issues discussed here to minimize the extent to which COIs can distort the scientific literature.

### Creation of bias and the nature of COIs

A COI occurs when individuals' personal interests are in conflict with their professional obligations. Often this means that someone will profit personally from decisions made in his or her professional role. The personal profit is not necessarily monetary; it could be progress toward the personal goals of the individual or organization, for example the success of a journal for a publisher or editor or the acceptance of ideas for a researcher. The concern is that a COI may bias behaviour, and it is the potential for bias that makes COIs so important. Before getting into the specifics of COIs, I will describe some of the re-

search on the biases we all have, the evidence that we are not always aware of our own biases, how biases can be created by vested interests and how people behave in response to revelations of COIs. The idea that scientists are objective seekers of truth is a pleasing fiction, but counterproductive in so far as it can lessen vigilance against bias.

A recent short review in *Science* asks how well people know their own minds and concludes the answer is not very well.<sup>3</sup> This is because "In real life, people do not realize that their self-knowledge is a construction, and fail to recognize that they possess a vast adaptive unconscious that operates out of their conscious awareness." Wilson and Brekke<sup>4</sup> reviewed some of the unwanted influences on judgments and evaluations. They concluded that people find it difficult to avoid unwanted responses because of mental processing that is unconscious or uncontrollable. Moore and Loewenstein<sup>5</sup> argue that "the automatic nature of self-interest gives it a primal power to influence judgment and makes it difficult for people to understand its influence on their judgment, let alone eradicate its influence." They also point out that in contrast to self-interest, understanding one's ethical and professional obligations involves a more thoughtful process. The involvement of different cognitive processes may make it difficult to reconcile self-interest and obligations. MacCoun,<sup>6</sup> in an extensive review, examined the experimental evidence about bias in the interpretation and use of research results. He also discussed the evidence and theories concerning the cognitive and motivational mechanisms that produce bias. He concluded that people assume that their own views are objective and "that subjectivity (e.g., due to personal ideology) is the most likely explanation for their opponents' conflicting perceptions." This is consistent with the suggestion of Platt, almost 50 years ago, that researchers' attachment to their own ideas results in competition among researchers rather than ideas.<sup>7</sup>

An early experimental study by Mahoney<sup>8</sup> is a particularly striking example of how researchers' bias can influence their

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behaviour. Reviewers were asked to referee manuscripts, all of which had identical methodology but reported different results. Reviewers were strongly biased against manuscripts that reported results that contradicted their own theoretical perspectives. This can have a deleterious effect as ideas that have long since been contradicted can persist in the literature.<sup>9,10</sup> Researchers' biases caused by preference for their own ideas can cause a serious COI when they present their own work and when they are involved in any aspect of peer review. Nonetheless, much more attention is paid to COIs owing to external influences such as money than to COIs related to researchers' inherent biases.

Cain and Detsky<sup>11</sup> reviewed some of the evidence on how biases can be created and how they can bias opinions in everyone. Experimental evidence supports the idea that "individuals use different strategies to evaluate propositions depending on whether the hypothesis is desirable or threatening/disagreeable to them." For example, a much higher proportion of people agree with the proposition that if someone sues you and you win the case the other person should pay your legal costs than with essentially the same proposition that if you sue someone and lose the case you should pay the costs. Cain and Detsky discuss some of the experimental work that demonstrates how people come to have biased opinions. For example, opinion can be biased by the first information encountered on a topic, a conclusion with obvious implications if the first information a physician or researcher learns about a drug is from the pharmaceutical company developing that drug. Experimental evidence also supports the idea that it is difficult to overcome the biases created by the effect of early information on beliefs. This explains why beliefs derived from experimental or epidemiological studies persist even after contradictory evidence from clinical trials provides more compelling contradictory evidence. Cain and Detsky suggest that "physicians have many relationships that may result in bias" — not just those involving pharmaceutical companies and not just those involving money — and warn that "such bias may be difficult to undo." The same conclusions surely apply to researchers. In another review, Dana and Loewenstein<sup>12</sup> describe the evidence indicating that gifts from industry can create bias. They conclude that self-serving bias prevents individuals from being objective even when they have a motivation to be objective; that instructions given to individuals about bias do not prevent them from becoming biased, suggesting a role for the unconscious in this process; and that self-interest alters the way individuals seek out and assess information.

One of the main strategies used to mitigate the effects of bias related to COI is disclosure. Most peer-reviewed journals require authors to make a COI statement that is often published with the article. The idea behind disclosure is that the reader of the article will be more skeptical about any claims made in the article. In an experimental study, different groups read a manuscript in which a COI was mentioned or not mentioned. Those reading the study with the mention of a COI considered the study to be less interesting and important.<sup>13</sup> However, given the evidence that people do not always know their own minds, these results have limitations. On the basis

of a review of the evidence on the effectiveness of disclosing COIs and on an experimental study, Cain and colleagues<sup>14</sup> concluded that disclosure may not always be useful for 2 reasons. First, those declaring a COI may feel entitled to deviate from what they consider objectivity because they have declared a COI. They may also exaggerate to overcome any diminished weight that the reader may put on what they have written. Second, those who read articles in which the author declares a COI may not discount biased information as much as they should because of a tendency to be influenced by information they know they should ignore and possibly because the act of disclosure may make them more likely to place greater weight on the author's statements given the author's openness in admitting to the COI. Whatever the reason, in some circumstances disclosure may result in the recipient of the biased information placing greater weight on the biased information.

A recent editorial in *Nature Medicine* discusses the difference between a perceived and an actual COI.<sup>15</sup> The editorial discusses the fact that the casual reader may consider there is a COI in sponsored content, but that because the "sponsors never have a say on the editorial content of anything [they] publish," and because the editorial content for supplements is already commissioned before potential sponsors are approached, any COI is apparent rather than real. However, as discussed, humans do not always know their own minds and are not always aware of their own biases. Articles may be commissioned to suit a particular sponsor's biases even without the person commissioning them being aware of that fact. In my opinion, it is not possible to state categorically that a COI is apparent rather than real.

All those involved in the research literature, including publishers, editors of journals, reviewers of manuscripts and authors, can have COIs. In the rest of this article I will discuss some of the factors that lead to COIs for each of these groups, describe how the *Journal of Psychiatry and Neuroscience* tries to deal with each of these issues and suggest how the current situation can be improved.

## The pervasiveness of COIs in publishing

Publishers are acting with a COI whenever they interfere with the day-to-day management of a journal by the editorial staff. Two extreme versions of this have come to light recently. According to a recent report in the *BMJ*<sup>16</sup> concerning a court case about the Merck anti-arthritis drug rofecoxib (Vioxx), Elsevier has apologized for the improper publication of Merck-sponsored marketing material "that was made to look like journals." More details are given in a report in *Nature Medicine*.<sup>17</sup> In a second case reported in *Nature*,<sup>18</sup> a computer-generated hoax article was submitted to *The Open Information Science Journal* published by Bentham Science Publishing. The paper was accepted and the authors were asked to pay US\$800 for publication. At this point the authors withdrew their manuscript. The editor-in-chief of the journal, when contacted by *Nature*, reported that he had not seen the article and stated that he would resign.

Several of the top medical journals are owned by medical

associations. As these journals often carry news and opinion items in addition to research reports there may sometimes be a conflict between the opinions of the editor of a journal and those of the officers of the association that owns the journal. Such conflicts have resulted in the departure of the editors of the *New England Journal of Medicine*,<sup>19</sup> the *Journal of the American Medical Association*<sup>20</sup> and the *Canadian Medical Association Journal (CMAJ)*.<sup>21</sup> The CMAJ is published by the Canadian Medical Association, also the publisher of the *Journal of Psychiatry and Neuroscience*. The firing of the editor of the CMAJ led to the Canadian Medical Association adopting 25 recommendations of a review panel that enshrine editorial independence in the governance structure of all journals published by the association.<sup>22</sup>

Given the cost of publishing, money is an important factor that can lead to COIs for publishers. This is true whether a publisher is for-profit or not-for-profit given that even not-for-profit publishers have to remain financially sound. The costs of publishing must be funded somehow, and the most common sources are journal subscriptions, advertising and publication charges. Advertising by drug companies is common in medical journals, and this is sometimes problematic. Othman and colleagues<sup>23</sup> did a systematic review of articles on advertisements in medical journals that included 24 articles assessing advertisements from journals in 26 countries. Although most of the advertisements made claims that were supported by a systematic review, meta-analysis or randomized controlled trial, some advertisements made claims that were not well supported by evidence. In some countries, most claims were not well supported. Another issue is that advertisements sometimes focus on the newest, most expensive drugs that may not be superior to cheaper alternatives.<sup>24</sup> One point of view is that medical journals should not accept advertising from industries relevant to medicine.<sup>24</sup> The alternatives, subscriptions and publication charges, also have their problems. The money spent on journal subscriptions by university and hospital libraries is not available for other purposes, and publication charges, which are usually paid from research grants, take away money that could otherwise be devoted to research. Thus, there is always a conflict between the publisher's interest in remaining financially sound and its responsibility to the researchers who provide the manuscripts and read the papers. A recent article in *Nature* (published by the Nature Publishing Group, a for-profit publisher) on one of the most prominent open-access not-for-profit publishers, the Public Library of Science (PLOS), gives an interesting perspective on publication charges.<sup>25</sup> The title of the article is "PLOS stays afloat with bulk publishing." The article states that the financial situation of PLOS has improved "thanks to a cash cow in the form of *PLOS One*," which "uses a system of 'light' peer review" and has generated substantial amounts of money from author fees. *PLOS One* reviews only for methodology, not for significance of the results, and minimizes costs by publishing only online. My own perspective is that this is an imaginative innovation that, in addition to being financially sound, may become an important model for publishing research. As the editorial board of *Nature* knows well, the significance of research

is sometimes hard to discern. *Nature* itself turned down the opportunity to publish the paper by Hans Krebs describing what Krebs called the citric acid cycle and everyone else calls the Krebs cycle.<sup>26,27</sup> The issue with publication charges, as with advertising, is how the COI is addressed. Policies related to advertising in medical journals are usually available, and a recent review summarizes some of those policies from 9 of the top medical journals.<sup>24</sup>

Publishers are capable of finding surprising ways to act inappropriately in the face of COIs. According to a recent report in the *BMJ*, Elsevier offered \$25 gift cards to academics to encourage them to post favourable reviews of the academic textbook *Clinical Psychology*, although subsequently Elsevier admitted this was a mistake.<sup>28</sup>

The *Journal of Psychiatry and Neuroscience* is an open-access journal that has no publication charge. Its main source of revenue is advertising in the print edition). The policies that govern advertising in the journal are available on the Canadian Medical Association website ([www.cma.ca/index.cfm/ci\\_id/25274/la\\_id/1.htm](http://www.cma.ca/index.cfm/ci_id/25274/la_id/1.htm)). For me as an editor, the important issues are that I have no contact with those who obtain advertising for the journal and do not know what advertisements will appear in any issue. The administrative staff ensures that advertisements do not appear in inappropriate places (e.g., an advertisement for an antidepressant next to an article on depression or antidepressants).

Conflicts of interest for editors are usually taken to mean conflicts related to funding from industry, and the *Journal of Psychiatry and Neuroscience* is among those journals that publishes this information on the journal website ([www.cma.ca/jpn](http://www.cma.ca/jpn)). However, in my opinion non-financial issues are probably more important. Every editor wants his or her journal to be a success. The measure of success of a journal that has become widely used, but is much criticized, is the impact factor. Acting in a way that will increase the impact factor of a journal is not always entirely compatible with the professional responsibilities of an editor.

The impact factor for a journal is based on the rate at which articles in the journal are cited. For example, the impact factor for 2008 is the sum of citations in 2008 to articles published in the journal in 2006 and 2007, divided by the number of articles published in 2006 and 2007. The number of citations a paper received can certainly be an indication of its importance. However, the relation between citations and importance is not a tight one. Obviously papers in a popular field will tend to receive more citations than those in a less popular field, irrespective of quality. This is an issue of some concern. In an important paper on "Why most published research findings are false," Ioannidis<sup>29</sup> discusses some of the factors that lead to false findings. He points out that, from a theoretical perspective, "the hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true." Pfeiffer and Hoffmann<sup>30</sup> have provided some empirical support for this prediction. In biological psychiatry research, one popular area is psychiatric genetics. Unfortunately, associations that are reported between particular gene polymorphisms and disorders or symptoms are often not replicated or confirmed by meta-analyses.<sup>31,32</sup> The false discovery rate may

be as high as 95%.<sup>33</sup> Interestingly, genetic association studies published in journals with a high impact factor are more likely to provide an overestimate of the true effect size owing in part to small sample sizes.<sup>34</sup> The *International Journal of Neuropsychopharmacology* demonstrated an interesting approach to the problem of non-replication in psychiatric genetic studies when it published a paper on the interaction between the 5-HTTLPR serotonin transporter polymorphism and environmental adversity and the risk for depression and anxiety.<sup>35</sup> In the same issue there was a review on the lack of replication in such genetic studies that suggested the former paper might provide "further evidence that the literature to date is compatible with chance findings."<sup>36</sup> All judgments about the quality of research papers are subjective. Nonetheless, an editor who selects for publication a psychiatric genetic study with a relatively small sample size and a level of significance not much better than 0.05 over an innovative and methodologically sound manuscript dealing with a topic that is not currently popular may be helping to enhance the impact factor of the journal at the expense of its scientific quality.

One direct way in which editors can manipulate impact factors is by altering the timing of publication of papers. If, for example, a paper that is likely to be highly cited was published in the December 2010 issue of a journal, citations that would contribute to the 2011 impact factor would have to occur within between 1 and 13 months after publication, but citations are unlikely to occur within 6 months of publication. If the same paper were published in January 2011, citations that occur between 12 and 24 months after publication would contribute to the 2012 impact factor. Thus, publishing papers that are likely to have a high citation rate early in any year will help to inflate the impact factor of a journal. Obviously this is unfair to authors if the publication of their paper is delayed, and I am not aware if it ever occurs. Nonetheless there is evidence that some editors do take estimated citation rates into account when making decisions. Chew and colleagues<sup>37</sup> analyzed impact factor trends for medical journals and interviewed the editors. They concluded that rising impact factors were due to deliberate editorial practices in spite of the editors' dissatisfaction with impact factors as the measure of the quality of a journal. One quotation from an editor is particularly salient: "our basis for rejection is often 'I don't think this paper is going to be cited.'" It is not clear from this quotation whether the editors would reject a manuscript because they thought the citation rate was more important than the quality of the science or because they equated the citation rate with the quality of the science.

Not all COIs for editors are related to impact factors. The desire of editors to please authors by having a manuscript reviewed as quickly as possible, thereby encouraging authors to submit further manuscripts, can be in conflict with getting excellent reviews. The assertion by Ioannidis<sup>29</sup> that much of what is in research journals is false can only be correct if standards of reviewing are not very good. Unfortunately this idea is supported by research. In a test of what errors peer reviewers detect, reviewers detected an average of 2.6 of 9 major errors in test manuscripts, and this number was not improved after reviewer training.<sup>38</sup> Serious statistical errors are common

even in some high-profile journals.<sup>39</sup> The best peer reviewers are usually busy people who will not necessarily be able to produce reviews promptly, and adding an expert statistical review to the content reviews may increase the time needed to review a manuscript. However, it is not possible to say to what extent, if at all, the poor standards of reviewing are due to the desire of some editors to speed up the process of review at the expense of the quality of the reviews.

Conflicts of interest for editors may also arise from the publication of supplements, the publication of papers by an editor, and the non-adherence to important guidelines for reporting. Journal supplements, which are often subsidized by the pharmaceutical industry, can help improve the financial standing of a journal, which is often a concern for editors and publishers. However a study concluded that manuscripts "published in journal supplements are generally of inferior quality compared with articles published in the parent journal."<sup>40</sup> Editors can legitimately publish a peer-reviewed article in the journal they edit as long as the manuscript undergoes peer review that is as thorough as all other manuscripts, and the member of the editorial board overseeing the peer review does his or her best to ensure that any bias in the assessment of the manuscript is minimized. This may not always be so. *Nature* recently reported on the editor of a theoretical physics journal who was facing growing criticism after publishing nearly 60 papers in 1 year in the journal he edited.<sup>41</sup> In terms of guidelines for reporting, many journals adhere to the statement of the International Committee of Medical Journal Editors ([www.icmje.org/publishing\\_10register.html](http://www.icmje.org/publishing_10register.html)). This requires that to be considered for publication clinical trials must be registered in a public trials registry at or before the onset of patient enrolment. However, some well-known journals in biological psychiatry publish the results of clinical trials without giving any information about trial registration, suggesting that the trials may not have been registered. One possible explanation for this is that the editors value the citations received by clinical trials, which are often highly cited, more than adherence to the trial registration policy.

Among the policies that the *Journal of Psychiatry and Neuroscience* has adopted to minimize any effect of editors' COIs are reporting of financial COIs of editorial board members on the journal website, publishing peer-reviewed papers in the order in which they were accepted (with the exception of including short commentaries on topical subjects or moving a shorter paper forward when a longer paper will not fit the page allotment of the journal), giving all published papers that contain statistics a full review by a statistician, not publishing supplements, ensuring that all papers from members of the editorial board go through full peer review and adhering to guidelines such as the registration of clinical trials.

Conflicts of interest for reviewers are, in part, similar to those for authors. If a manuscript discusses medications and a reviewer has some connection with a pharmaceutical company that is involved with any medication mentioned in the manuscript or a drug of the same class produced by a competitor, this COI should be mentioned to the editor; the *Journal of Psychiatry and Neuroscience* asks reviewers to mention any COI to the editor. Other COIs for reviewers are less clear

and are, in my experience, seldom mentioned. These include any possible personal relationship (positive or negative) with any of the authors of a manuscript and professional rivalry owing to the reviewer and authors researching similar topics. Reviewers have their own biases based on their own research approaches. In my experience, if a reviewer recommends that the authors cite an additional reference, more often than not it is to one of the reviewer's own papers, and the recommendation is not always appropriate. An important COI for reviewers is the conflict between the professional obligation to produce a well thought-out review in a timely manner and the desire not to spend too much time on a task that is relatively thankless. Reviewers seldom read the instructions on what is required in a review. The editor of *Obstetrics and Gynecology* inserted the following sentence in the middle of a paragraph of instructions for reviewers: "If you read this and call or fax our office, we will send you a gift worth 20 dollars."<sup>42</sup> The response rate was 17%. A minority of reviewers who agree to review a manuscript never submit their reviews or clearly do not devote the time needed to their reviews. The latter is readily apparent when, for example, a reviewer's assessment includes factual errors about the design of the study. Behaviours like this inconvenience editors and can adversely impact authors by delaying decisions on manuscripts.

Little research has been done on the factors that influence reviewers' decisions, and more is needed so that editors can take into account possible biases in reviewers' assessments. As mentioned, reviewers miss many important flaws in manuscripts, and training does not improve this situation.<sup>38</sup> In ecology research, recommendations to reject are not influenced by age, but those who have more papers in high-impact journals recommend rejection of manuscripts at up to twice the rate of reviewers with few or no papers in high-impact journals.<sup>43</sup> Although this is an indication of different biases among different authors, it does not necessarily reflect a COI.

The COIs of authors include those conflicts that have potential to affect how the research was conducted and interpreted as well as those that influence how it is presented, which is why financial COIs for authors are an important issue. A review of studies on the extent, impact and management of financial COIs reported a significant association between industry sponsorship and pro-industry outcomes in published papers and concluded that financial ties between industry and academia influence biomedical research in important ways.<sup>44</sup> This is consistent with the idea discussed earlier in this editorial that admitting to a financial COI does not necessarily deal with the bias that the financial COI creates. The issue of what exactly constitutes a financial COI can be complex. The website of the National Institutes of Health (NIH) in the United States on frequently asked questions about financial COIs is more than 5,000 words long (<http://grants.nih.gov/grants/policy/coifaq.htm#c1>). However, the bottom line is that NIH requires anything over \$10 000 per year to be declared. This may seem high to some, but GlaxoSmithKline recently announced that they would limit the advisory payments and honoraria it gives to US doctors to (only?) \$150 000 per year.<sup>45</sup> Some journals require any financial COI to be declared, no matter how small. Although

payment of a \$500 honorarium may not create as big a bias as a \$50 000 consultant payment, it is unrealistic to think that researchers might mention the exact amount of payments when declaring COIs.

Because financial COIs have been the subject of many recent articles, this editorial focuses on other COIs that authors should be attempting to deal with. The first, and by no means trivial, COI that is an issue for the vast majority of authors is the pride and sense of ownership that authors take in the work they submit for publication. This presumably is responsible for the fact that when authors were interviewed about their published papers "important weaknesses were often admitted on direct questioning but were not included in the published article."<sup>46</sup> Certainly editors are used to asking authors to mention the limitations of their studies and to be more cautious about the implications of the research. Another related factor is the desire for researchers to advance their careers and get recognition from their peers. Research suggests that social and monetary reward may work through both psychological<sup>47</sup> and neuroanatomical processes<sup>48</sup> that overlap to some extent. The big difference in relation to COIs is that social rewards, unlike monetary rewards, cannot be disclosed in any meaningful way.

In some situations COIs can arise because all the authors need to take responsibility for the content of a manuscript. If an author is included who does not fulfill the requirements of the International Committee of Medical Journal Editors for authorship ([www.icmje.org/ethical\\_1author.html](http://www.icmje.org/ethical_1author.html)), then both that person and the other authors are not fulfilling their professional obligations. Another related problem is that of ghost authorship (i.e., when someone who was not involved in the work, often a pharmaceutical company employee, writes a manuscript but does not appear as an author; see Ross and colleagues<sup>49</sup>). Ghostwriting may be part of a pharmaceutical company effort to promote products through "carefully orchestrated campaigns to pass off sympathetic, if not biased, research and review articles as the work of academic scientists rather than of their own contracted employees."<sup>50</sup> Finally, there may be conflict among the different authors in how to present and interpret the results of a study. Attempts to resolve these issues are not always successful. Interviews of authors of papers published in *The Lancet* revealed that individual authors often disagreed with opinions expressed in the papers and that the papers revealed "evidence of (self)-censored criticism, obscured meaning, and confused assessment of implications."<sup>46</sup> Overall, the evidence suggests that non-monetary COIs can create similar problems to monetary ones.

The *Journal of Psychiatry and Neuroscience* asks all authors to sign a statement about any financial COIs they may have, state what role they played in the research and writing of the manuscript, state whether they approved the final version of the manuscript, and indicate whether there was anyone involved in writing the manuscript who was not an author.

In spite of all the problems created by bias and COIs, research continues to advance. However, the speed of the advance might be enhanced if these problems could be reduced. Obviously there needs to be better training and

mentoring of scientists concerning COIs and bias. Unfortunately, a recent study on the effects of mentoring and training in responsible conduct of research concluded that these interventions have the potential to influence behaviour in ways that can both increase and decrease the likelihood of problematic behaviour.<sup>51</sup> More research on effective training and mentoring techniques is needed urgently. Fortunately, some relevant information is available in the psychology literature. In experimental studies, for example, asking participants to consider the opposite of their own opinion was more effective in reducing their biases than asking them to be as fair and unbiased as possible without giving them a specific strategy to achieve this aim.<sup>52</sup>

The investigations of Senator Charles Grassley have intensified the debate about sources of bias in the literature and how they may be reduced. However, the debate has focused rather narrowly on money and the objective of a literature relatively free of bias remains a pious but distant hope.

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