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General Commentary

Bad Science: Cause and Consequence

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ABSTRACT

Scientific progress is dependent on accumulation of quality data with appropriate data analysis. Unfortunately, there are a troubling number of accounts describing an inability to replicate published work. Some explanations are lack of access to proprietary reagents and equipment, or lack of expertise and know how. However, it is clear that there are many publications that are fatally flawed, and it is difficult to ascertain which ones they are, but there are clues. Many articles are improperly controlled, resulting in false-positive or -negative results. Reagents and procedures are used without verifying their specificity. There is also confirmation bias, a tendency to seek and find conclusions that we like, which is exacerbated by faithful acceptance by readers of the publication record without assessment of merit. These and other issues have slowed progress, resulted in waste of scarce funds, and even put patients at risk when clinical decisions are made according to flawed data. Solving these and related problems requires recognition of the problem and better training. We also need to take personal responsibility for not only our own work, but also for the accuracy of information in the scientific domain.

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Introduction

Scientists have been making steady and remarkable progress in solving key questions. Importantly, we are training new scientists who will use the current findings to identify new breakthroughs. Unfortunately, a number of reports[1-7] describe an inability to reproduce published results, with failure rates as high as 90% (Table 1). Surprisingly, the reproducibility of published data did not significantly correlate with journal impact factor,[2] and even results from prestigious research units could not be duplicated. It is important to note that there are many reasons that findings are not reproducible. Reagents, animals, or cell lines may be unique to the groups that first reported the findings. Skills and knowledge are not easily transferable to other laboratories. However, these cannot completely explain the findings. We must conclude that many reports are wrong.

Correcting mistakes is difficult, and some flawed hypotheses can persist for years or decades. Some hold that vaccines cause autism, although the original 1998 article[8] suggesting a relationship with vaccines was immediately challenged and retracted in 2010. In a controversial 1989 study, Fleischmann and Pons reported that they had discovered a method to produce cold fusion energy,[9] but the results were not replicated by multiple groups, and there was no plausible mechanism that could explain their results. Despite these problems, researchers continued to publish articles supporting the cold fusion proposal, with fundraising requests to do follow-up experiments. Today, offers of investment opportunities to develop new devices based on the original hypothesis still exist.

The consequences of faulty articles are substantial. An entire field can converge to the wrong answer. We are certainly wasting scores of research dollars, and delaying or even halting progress. Every day spent on an invalid theory is one less day spent on a more promising one. Regulatory agencies are making decisions on medications and procedures with flawed data in hand. We may be giving false hope, treating patients improperly, or even putting patients at risk when clinical trials are initiated according to unsound hypotheses. Indeed, there is a difficulty in translating preclinical data into positive results in clinical trials, in part because of the poor quality of the supporting animal data.[10,11] The problem is so deep and profound that to some it is not clear which, if any, articles can be trusted. It is clear that we must address the problems, but to do that, we need to understand the causes.

Poor Experimental Design and Use of Bad Reagents Are Common Features of Irreproducible Data

In studies that are not reproducible, experiments may be performed that do not include appropriate controls to catch

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Table 1
Poor Reproducibility of Published Articles

Report	Field of Science	Reference
0/8 drug treatments in ALS studies repeated	Neuroscience	Scott (2008)[1]
75%-80% of 67 studies not reproduced	General Medicine	Prinz (2011)[2]
90% of 53 studies not reproduced	Oncology	Begley (2012)[3]
6 of 12 spinal injury studies not replicated	Neuroscience	Steward (2012)[4]
31/34 studies on animal autism were inconclusive	Neuroscience	Lasic (2013)[5]
55% unable to reproduce published data	Oncology	Mobley (2013)[6]
61 of 100 studies did not replicate	Psychology	Open Science Collaboration (2015)[7]

false-positive and false-negative results. Alternatively, the strategies used may promote questionable conclusions. These may be used because other more effective measures failed. For example, experiments may be performed that generate indirect evidence. Thus, the mechanisms are inferred and inconclusive. Correlations may be found that are merely statistical aberrations. For example, the correlation between per capita margarine consumption and divorce rate in Maine (http://www.tylervigen.com/spurious-correlations) does not mean there is a causal relationship.

Another recurring problem is bad reagents which may be nonspecific or otherwise not suited to the task. In addition, reagents may have contaminants that cause artifacts. Berglund et al.[12] reported that half of the 9000 antibodies used for tissue profiling had staining patterns inconsistent with other data sources such as bioinformatics, and only 7% had a high validation score. Antibodies are the workhorse of many studies, yet the antibody reagent problem is not appreciated. Small-molecule inhibitors by their very nature can have off-target effects. Failure to demonstrate specificity renders any study using them uninterpretable.

These and related issues are often not caught by the peer-review process, and bad science is published. Subsequent correction of errors may not occur when there is too much trust in the publication record. Thus, invalid theories may be retested with the same improper protocols and strategies thereby "validating" the original flawed data and conclusions.

Bias Can Promote Bad Science

Confirmation bias[13] (the unwitting tendency to search for, interpret, favor, recall, and mold information in a way that confirms one's beliefs or hypotheses) is deeply rooted in many people, including scientists. Symptoms of this bias are selective reporting of, or even falsifying of data. Conflicting data is minimized or reported as "data not shown." Researchers may also perform a number of experiments, each of which is inconclusive, yet which "taken together" lead them to a questionable conclusion. There is also selective citing of supportive references. Of particular concern is when authors vigorously defend their articles in the face of mounting evidence against their positions. Manipulations like these plague so many studies that one scientist concluded that most published research findings are false.[14]

A bias toward publication of positive data was recognized as early as 1979.[15] This bias is partly explained by the view that a positive result "trumps" negative data. Thus, a single positive result can be considered definitive in a sea of negative data. In addition, journals favor publication of positive and novel results. These are usually supportive of the popular view, which provides a disincentive to perform repeat experiments. Thus, positive results are more likely to be published, and remain unchallenged.[16]

The EPOR Story

Problems and causes of irreproducibility are highlighted by an analysis of articles examining a role of erythropoietin (EPO) in cancer. EPO is a glycoprotein hormone produced by the kidney that is the primary regulator of erythropoiesis, red blood cell formation. Cloning of the *EPO* gene and regulatory approval and marketing of recombinant human EPO (rHuEPO) and other erythropoiesis-stimulating agents (ESAs) allowed for pharmacological correction of anemia. In a 2003 anemia correction trial, locoregional progression-free survival of patients with head and neck cancer was poorer with ESA (epoetin B) than with placebo.[17] The authors subsequently proposed a mechanism. ESAs might enhance tumor progression by binding and activating EPO receptors (EPORs) on tumor cells,[18] thereby promoting their growth and survival. Subsequently, numerous publications appeared suggesting EPOR was widely and highly expressed in cancer cells and that ESAs promoted tumor cell growth and survival *in vitro*. This proposal was disputed according to other studies suggesting that ESAs had a singular effect on erythropoiesis and that EPOR was expressed exclusively in the erythroid compartment.[19]

To evaluate the quality of the work around this hypothesis, a literature search was done and 220 ESA/EPOR articles that described preclinical *in vitro* or animal data, or experiments with human tumor samples, were identified. The methods and results sections of each article were evaluated, as were the conclusions. The conclusions were considered questionable if the articles had one or more of the following: use of nonspecific antibodies or other reagents, they lacked positive and negative controls to detect false-positive or false-negative data, or the data did not support the conclusions. Ninety percent (198) of the 220 articles failed one or more of the tests (Fig. 1). The author conclusions were divided into 2 categories; 144 articles supported the EPOR-cancer hypothesis and 76 were neutral or did not. All of those supporting the hypothesis failed one or more quality tests. The failure rate was also high for those not supporting the hypothesis, but 22 were considered adequately executed. It is important to note that this analysis does not address the EPOR—cancer question per se; other information is required. However, it does raise concerns about the quality of the published work and, at a minimum, offers an explanation for why there was so much conflicting data.

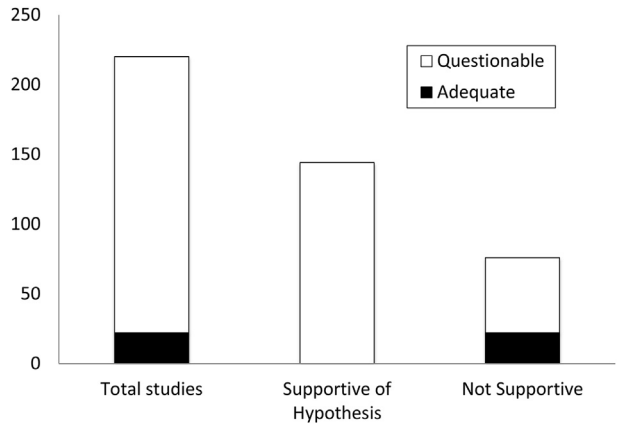

Figure 1. Reliability of conclusions from "Epo-EpoR and cancer" articles. Articles (220) were identified according to literature searches that tested the hypothesis that ESA might have a direct effect on promoting cancer cell growth or survival. Each article was examined to see if they included EpoR-positive and -negative control cell types, used antibodies and inhibitors that were demonstrably specific to the target, and whether the data supported the conclusions. Those failing one or more of those criteria were considered questionable. The number of articles whose conclusions supported the EpoR hypothesis and those that were neutral or didn't support the hypothesis are shown.

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