Teaching Rigor and Reproducibility in Research

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Is this a new problem?

“Reviewers have asked him to reproduce the experiment.”
“...try those experiments very carefully, and more than once, upon which you mean to build considerable superstructures either theoretical or practical, and to think it unsafe to rely too much upon single experiments...”

Certain Physiological Essays, 1661
The scandal of poor medical research

We need less research, better research, and research done for the right reasons.

What should we think about a doctor who uses the wrong treatment, either wilfully or through ignorance, or who uses the right treatment wrongly? Such a view is based on the assumption that such behaviour is rare. Unfortunately, that assumption is false. In a recent study published in the BMJ, I showed that many doctors in the UK are not using drugs properly.

What, then, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. 1-7 This is surely a scandal.

Is there a Data Crisis?

Mainstream attention

- Bayer (2011, *Nature*) <25% of 53 preclinical studies
- Reproducibility Project (2015, *Science*) 36 of 100 papers in psychology
- NIH policy change for preclinical research (Collins & Tabak, 2014 *Nature*)
<table>
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<tr>
<th><strong>Individual researchers</strong></th>
<th><strong>Institutions</strong></th>
<th><strong>Publishers</strong></th>
<th><strong>Funders</strong></th>
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<td>- Fail to collaborate or share data</td>
<td>- Implement policies that reward researchers based <em>only</em> on grant income or publication record</td>
<td>- Focus on perceived novelty or impact</td>
<td>- Reward novelty or perceived positive outcomes without considering rigor</td>
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<td>- Fail to keep detailed records or report detailed methods</td>
<td>- Selectively interpret data or publish only results consistent with a hypothesis</td>
<td>- Fail to offer or encourage proper training</td>
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<td>- Selectively interpret data or publish only results consistent with a hypothesis</td>
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<td>- Fail to consider replication studies, negative results, and other vital forms of scientific discourse</td>
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<td>- Be overly lenient about teaching best practices to trainees</td>
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<td>- And so on!</td>
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How do we address this?

• T32 supplement from NIGMS to develop online course *Rigor and Reproducibility in Research* (3R)
• Appointed a “Reproducibility Czar” and course director, Dr. Kenneth Witwer
  – Alyssa Ward, PhD student (BCMB)
  – John Porter, formerly of NINDS
  – Megan Thorpe, Office of Online Education
• Course is freely available on JHU *myLearning* platform
• Plans to upload on LMS platform like Docebo
Online Modules

• Introduction
• Experimental Design
• Authenticating and Validating Reagents
• Recording and Reporting Data
• Sex as Biological Variable*
• Data Processing and Presentation
• Trends in Publishing

Small Group Discussion

• In Class Discussion
• Journal Clubs
• Panels

*In progress
Next, what about replication and reproduction? Is there a difference? Indeed, we can make a valid distinction. However, it is important to note that the words replication and reproduction are sometimes used interchangeably. Replication refers to an exact copy: making a "replica". If a study has been replicated, it has been done over in exactly the same way. A study is replicable only if the experimental
Dr. X reads an interesting paper on a novel drug to block a cellular receptor involved in disease. The drug has been studied in vitro with rigorous methods. Dr. X wishes to test the drug in her mouse model of disease. Would Dr. X's investigation be a reproduction or replication study? Click either button below to make a choice.

**Replication study**

That's right! This would be a “reproduction” study because Dr. X is altering a major variable of the experiment (mouse disease vs. in vitro).

**Reproduction study**

Let's test your knowledge. Dr. X reads an interesting paper on a novel drug to block a cellular receptor involved in disease. The drug has been studied in vitro with rigorous methods. Dr. X wishes to test the drug in her mouse model of disease. Would Dr. X's investigation be a reproduction or replication study?
Scenario: 16 mice receive a drug intravenously, while 16 control mice receive drug vehicle only.

Select what each of the follow-up approaches below are describing.

**Do the experiment again with different mice.**
- Direct replication
- Systematic reproduction
- Conceptual reproduction

Correct! A new dataset is being generated, with exact replication of experimental conditions and variables.

**Re-do with a different dose or administration route.**
- Direct replication
- Systematic reproduction
- Conceptual reproduction

Correct! We’re using the same system as the original experiment, but altering key variables.

**Try the drug in a stem cell model, or in a human trial.**
- Direct replication
- Systematic reproduction
- Conceptual reproduction

Correct! We’re translating the original findings into a different system.

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Authenticating Reagents

In 2008, an analysis of 40 human thyroid cancer cell lines revealed many instances of cross-contamination. Click to hear from Dr. Martha Zeiger about how they made this discovery and why it was so important.

Please review all 4 examples before moving on.
Emphasize 3R Throughout Training

• Require Standard Operating Policy for Data Management
• Journal club discussion, poster presentations, research talks
• Thesis meeting and written thesis
• Paper writing workshop for years 3-5
  -- Open science, preprints, transparency in research reporting, best practices in data presentation
R³ISE approach in a nutshell

Bosch & Casadevall, 2017, mBio
Bosch, 2018, Nature

Casadevall & Fang, 2016, mBio
R³ISE provides a structured approach to graduate science training in critical thinking & good investigative practice.
R³ISE training modules can be flexibly integrated into a variety of graduate science curricula, e.g. JHMI’s CMM: