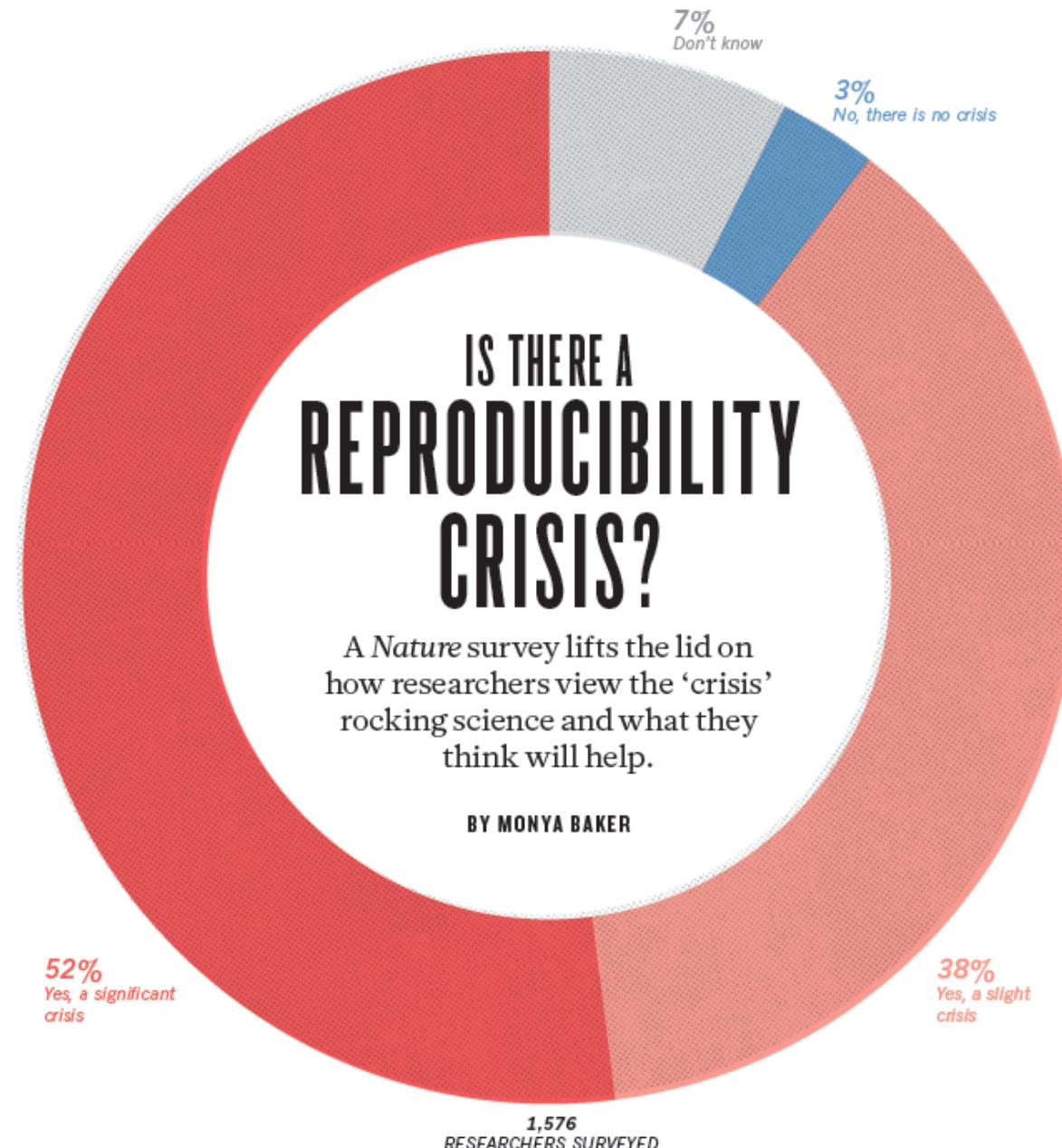


Reproducibility Crisis

Cooduvalli Shashikant

Co-Director, Bioinformatics and Genomics Graduate Program

IS THERE A REPRODUCIBILITY CRISIS?



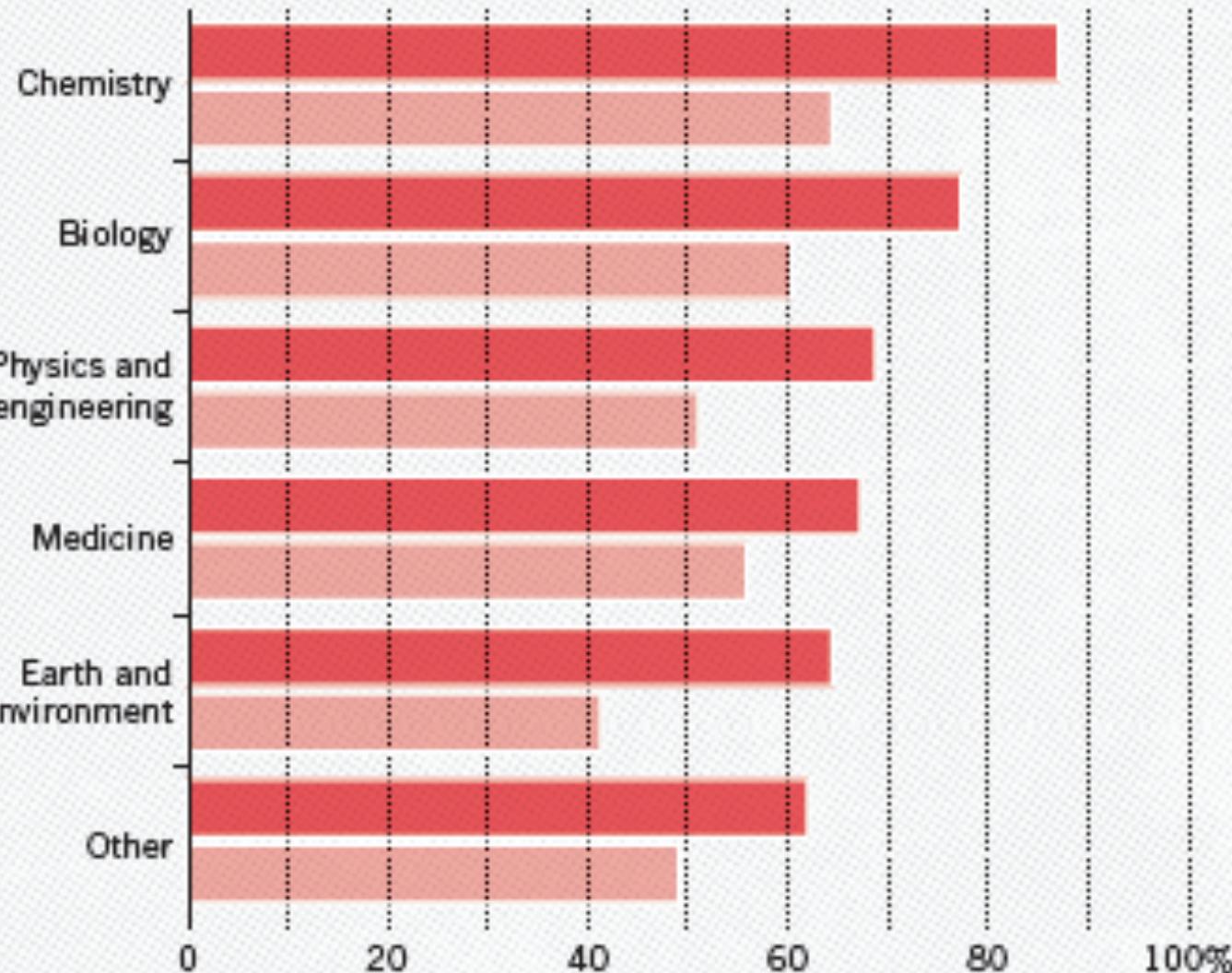
HAVE YOU FAILED TO REPRODUCE AN EXPERIMENT?

- Some one else's
- Your own

HAVE YOU FAILED TO REPRODUCE AN EXPERIMENT?

Most scientists have experienced failure to reproduce results.

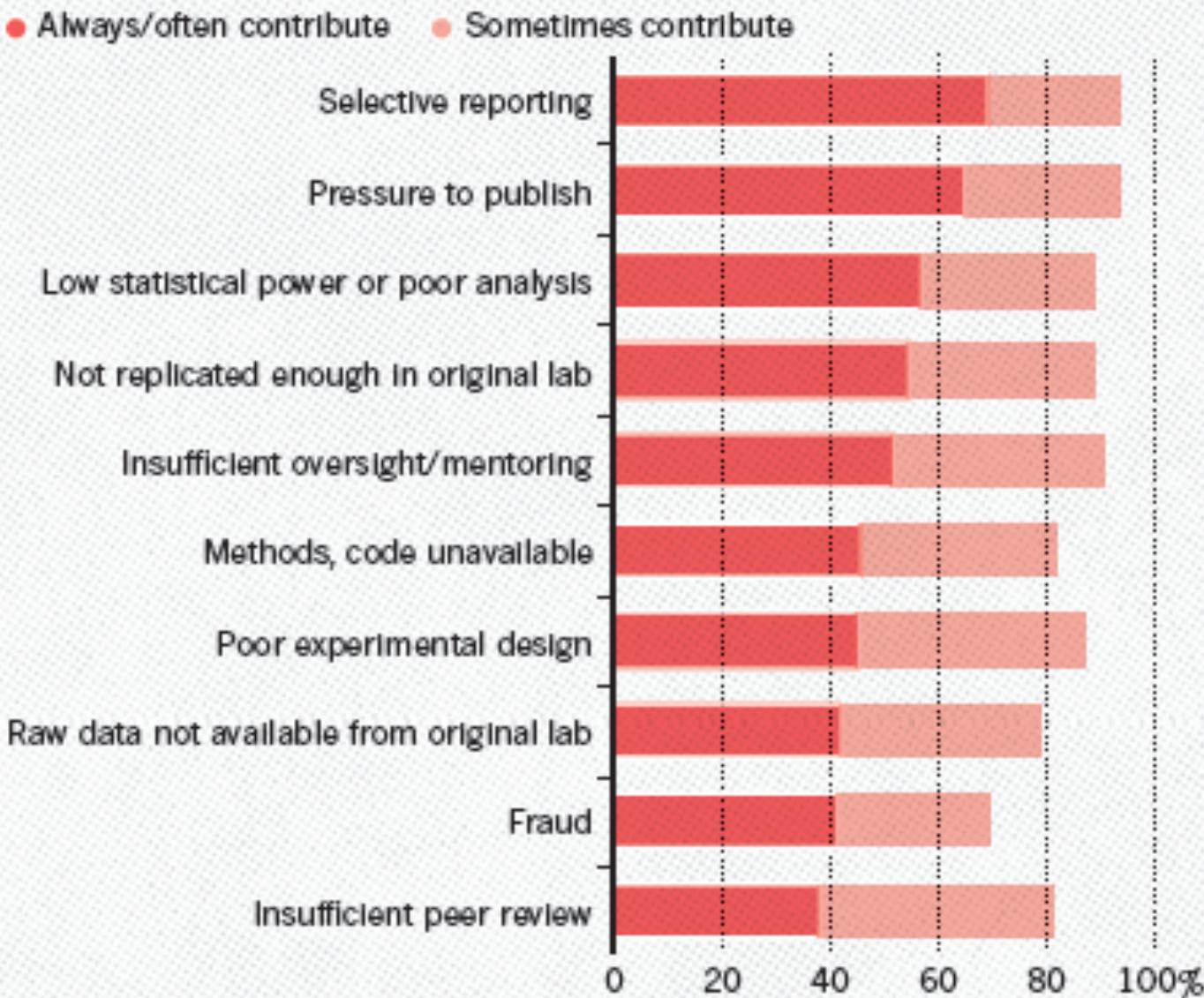
● Someone else's ● My own



WHAT FACTORS CONTRIBUTE TO IRREPRODUCIBLE RESEARCH?

WHAT FACTORS CONTRIBUTE TO IRREPRODUCIBLE RESEARCH?

Many top-rated factors relate to Intense competition and time pressure.

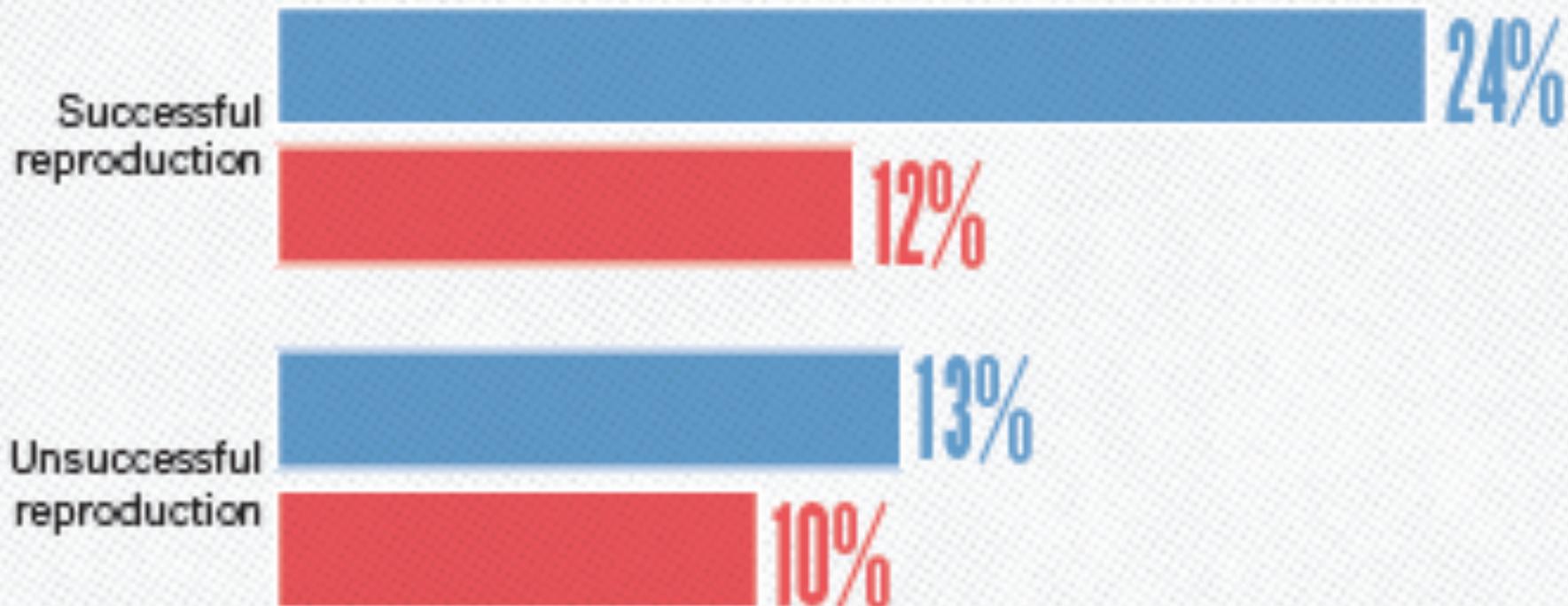


HAVE YOU EVER TRIED TO PUBLISH A
REPRODUCTION ATTEMPT?

HAVE YOU EVER TRIED TO PUBLISH A REPRODUCTION ATTEMPT?

Although only a small proportion of respondents tried to publish replication attempts, many had their papers accepted.

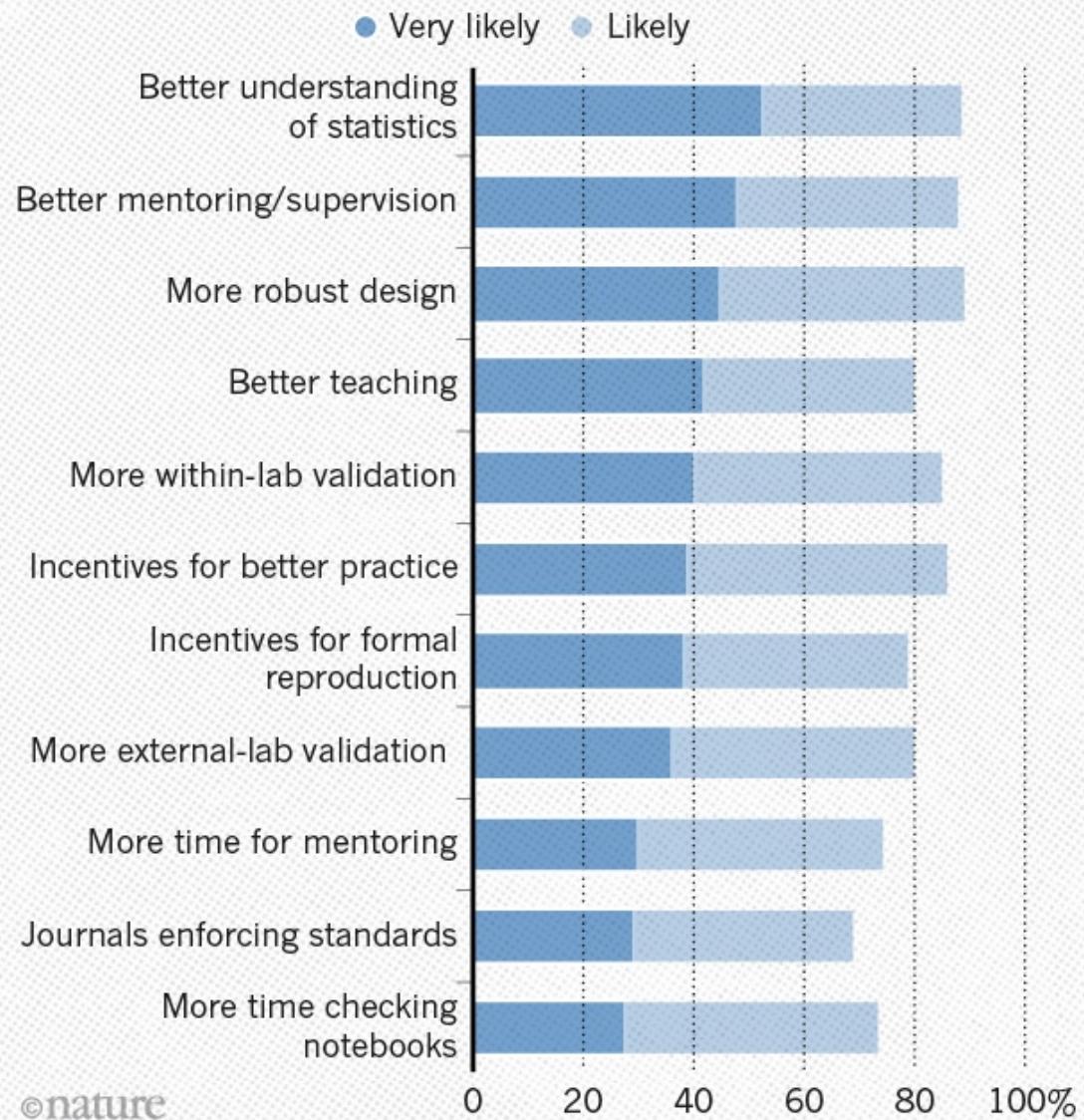
- Published
- Failed to publish



WHAT FACTORS COULD BOOST REPRODUCIBILITY?

WHAT FACTORS COULD BOOST REPRODUCIBILITY?

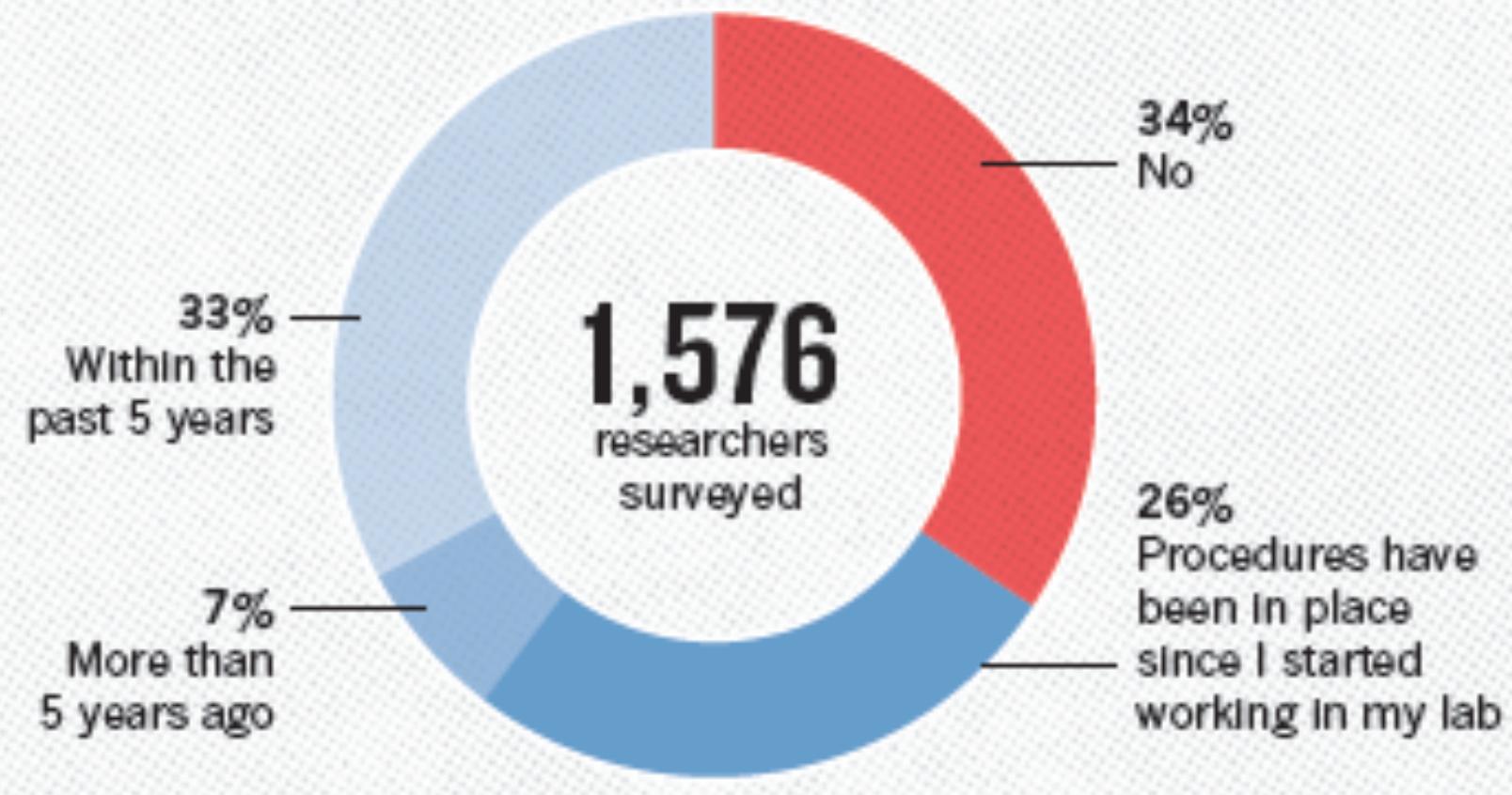
Respondents were positive about most proposed improvements but emphasized training in particular.



HAVE YOU ESTABLISHED PROCEDURES
FOR REPRODUCIBILITY?

HAVE YOU ESTABLISHED PROCEDURES FOR REPRODUCIBILITY?

Among the most popular strategies was having different lab members redo experiments.



The NIH initiative

- Students may not be receiving adequate training early in graduate school in experimental design and other skills related to conducting rigorous and reproducible research'

Training grants

- Training grants, Career Development and Individual fellowships will require formal instructions in
 - Rigorous experimental design
 - Transparency to enhance reproducibility
- Boot camp supported under ‘Administrative supplements to NIGMS Predoctoral Training Grants (PA-15-136)’
- PSU commitment to conduct boot camp for next five years

NEW GRANT GUIDELINES

what you need to know

WHY UPDATE THE GUIDELINES?

The updates focus on four areas deemed important for enhancing rigor and transparency:

1

PREMISE

The scientific premise forming the basis of the proposed research

2

DESIGN

Rigorous experimental design for robust and unbiased results

3

VARIABLES

Consideration of relevant biological variables

4

AUTHENTICATION

Authentication of key biological and/or chemical resources

Send inquiries to
reproducibility@nih.gov

See also NIH Notice NOT-OD-16-011
<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>

WHAT ARE THE UPDATES?

1 UPDATES TO RESEARCH STRATEGY GUIDANCE



The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:

The new research strategy guidelines require that you:

- State the strengths and weakness of published research or preliminary data crucial to the support of your application
- Describe how your experimental design and methods will achieve robust and unbiased results
- Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

2 NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These include, but are not limited to:



Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.

- DO NOT** put experimental methods or preliminary data in this section
- DO** focus on authentication and validation of key resources

3 NEW REVIEWER GUIDELINES

Here are the additional criteria the reviewers will be asked to use:

→ Is there a **strong scientific premise** for the project?

→ Have the investigators presented adequate plans to address **relevant biological variables**, such as sex, for studies in vertebrate animals or human subjects?

→ Have the investigators presented strategies to ensure a **robust and unbiased approach**, as appropriate for the work proposed?



Reviewers will also be asked to comment on that new attachment (see Update 2)!

<http://grants.nih.gov/reproducibility/index.htm>

Sources of Lack of Reproducibility

Sources of Lack of Reproducibility

- Fabrication, Falsification, plagiarism, misconduct
- Inadequate measures for data quality and reproducibility
- Biased reporting of results
- Inappropriate analysis
- Incomplete description of methods

Historic cases of Scientific Misconduct

- Charles Darwin
 - Origin of Pose: Saying ‘Cheese’ for Darwin NY Times, April 25, 1998
<http://www.nytimes.com/1998/04/25/books/origin-of-the-pose-saying-cheese-for-darwin.html>
- Louis Pasteur
 - Pasteur and culture wars, an exchange, The New York Review of Books, Dec 21, 1995; http://www.nature.com.ezaccess.libraries.psu.edu/search/adv_search?sp-q-1=nature.news
- Gregory Mendel
 - Beyond the Mendel-Fisher Controversy, Science, 350, 159, 2015,
<http://www.sciencemag.org.ezaccess.libraries.psu.edu/content/350/6257/159.full?sid=db800037-6596-432a-a00b-50bbe9d59686>

Fraud/Misconduct

- Mark Spector
 - <https://www.the-scientist.com/?articles.view/articleNo/26694/title/My-Favorite-Fraud/>
- Where are they now
 - <http://www.nature.com.ezaccess.libraries.psu.edu/articles/445244a>
- Scientific Misconduct, Ann. Rev. Psychology, 67, 693, 2016
 - <http://www.annualreviews.org.ezaccess.libraries.psu.edu/doi/full/10.1146/annurev-psych-122414-033437>

Fabrications



- William Summerlin (1974) Memorial Sloan-Kettering Research Institute
 - Transplant research: expected change in coat color; drew patches on mice with a black marker pen

How common are fraud, fabrication and falsification?

- 1-2% in anonymous survey admit falsification of data
- Much higher percentage admit dropping a data point or not publishing contradictory results
- Questionable research practices are much higher

Misrepresentation and Distortions

- More common than fraud, fabrication, falsification, plagiarism and misconduct of research

Concept of spin

“a form of propaganda, achieved by providing a biased interpretation of an event or campaigning to persuade public opinion in favor of or against some organization or public figure”



Spin

- A specific reporting that fails to faithfully reflect the nature and range of findings and that could affect the impression that the results produce in readers, a way to distort science reporting *without actually lying*
- Conscious, unconscious and unintentional
- Legitimate in some contexts
- In others, may create inaccurate impression of the study results

Spin

- The consequence of a lack of understanding of methodologic principles
- A parroting of common practices
- A form of unconscious behavior
- An actual willingness to mislead the reader
- Favors the author's vested interest (financial, intellectual, academic, and so forth)

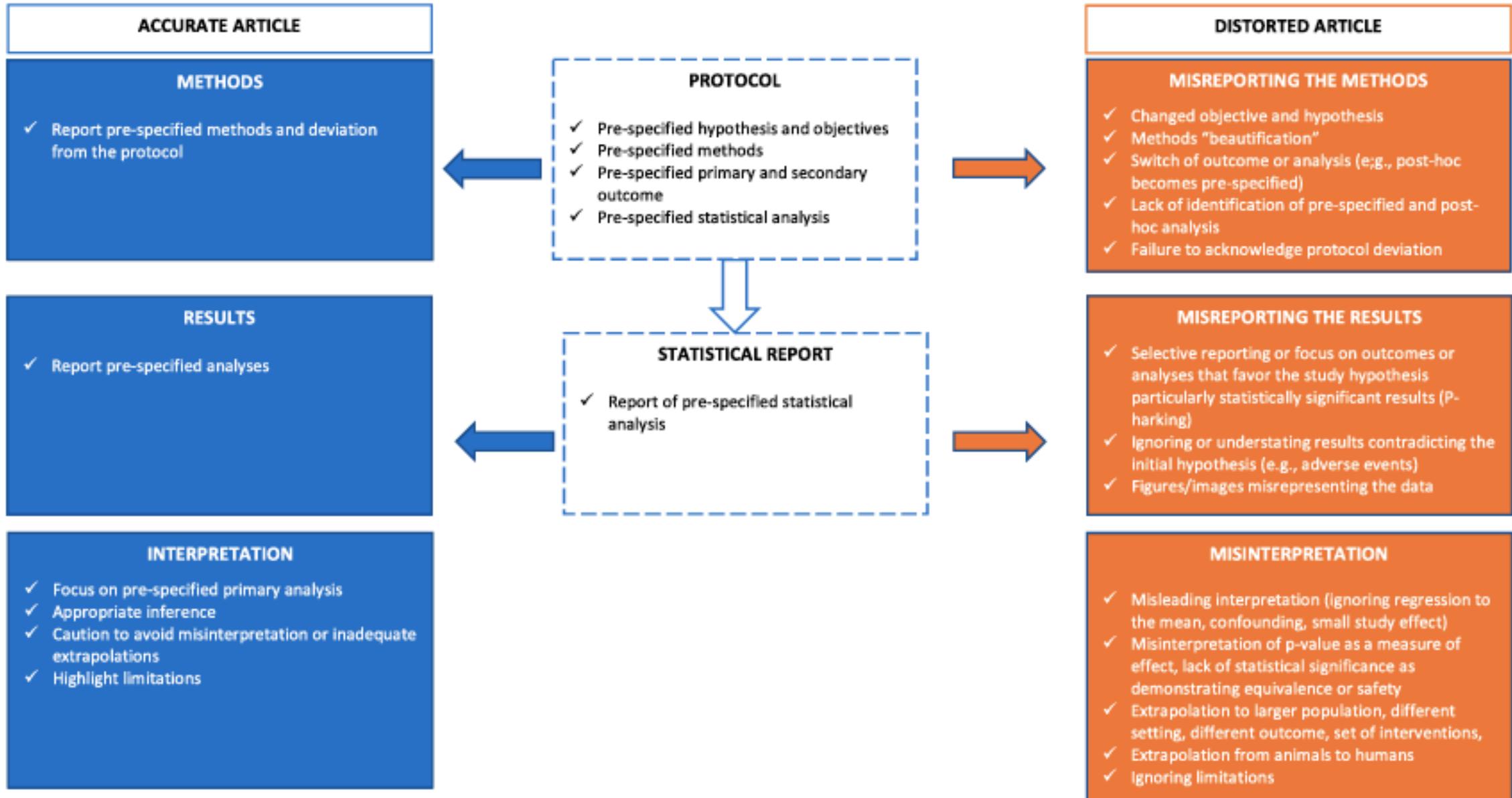
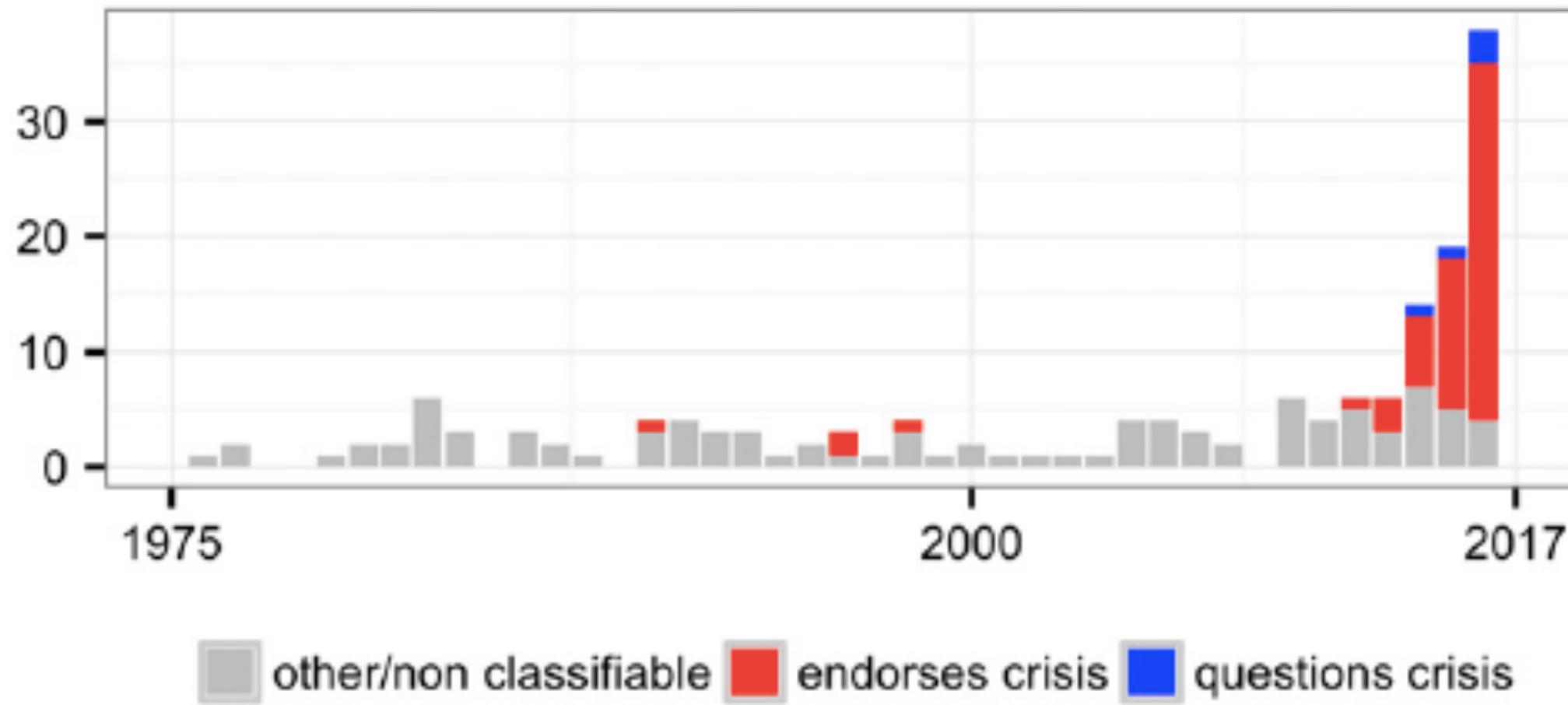


Fig. 1. Practices of spin in published reports.

Is science really facing a reproducibility crisis, and do we need it to?

Daniele Fanelli^{a,1}

Frequency of Crisis Narrative in Web of Science Records



- Published studies are getting longer, more complex and *richer in data*
- *Negative results* are increasingly getting embedded in longer publications
- *Globalization* of research is contributing to the rise in scientific misconduct in publication
- Rising power of information and communication technologies are transforming *scientific practices*

Reproducibility failures are essential to scientific inquiry

A. David Redish^{a,1}, Erich Kummerfeld^b, Rebecca Lea Morris^c, and Alan C. Love^d

Scientific Progress

- Observation
 - Theory
 - Replication
 - Failure
 - Re-integration
-
- *There is a widespread misunderstanding about the role of reproducibility in science*

Reproducibility and Scientific Progress

- Karry Mullis
 - Polymerase Chain Reaction
- Beatrice Mintz
 - Chimera of mouse embryonic cells +teratoma cells
 - Pluripotent stem cells
- Carl Illmensee
 - Cloning experiment
 - Imprinting: Surani, Solter
 - Vindicated?
- Rudolf Jaenisch
 - Reproduced important results of mouse cloning, induced pluripotent stem cells (iPS)



Fig. 1. Discussions about a “reproducibility crisis” often ignore what takes place when reproducibility fails: the integration of conflicting observations and ideas into a coherent theory. Image courtesy of Dave Cutler (artist).

Reproducibility Failures

- Time necessary to reconcile conflicting results
- Attention to the process of reconciling conflicting results
- Synthesis of diverse perspectives to be encouraged
- Theoretical integration leads to reliable results

Scientific Progress

- Scientific discovery is an observation in under a given set of conditions
- When unable to replicate, one focuses on determining hidden variables
- Over a given time diverse outcomes including reproducibility failures get incorporated into a broader account

Failure to Generalize

In many of these cases, what have been called “failures to replicate” are actually failures to generalize across what researchers hoped were inconsequential changes in background assumptions or experimental conditions.

Scientific progress despite irreproducibility:
A seeming paradox

It appears paradoxical that science is producing outstanding new results and theories at a rapid rate at the same time that researchers are identifying serious problems in the practice of science that cause many reports to be irreproducible and invalid.