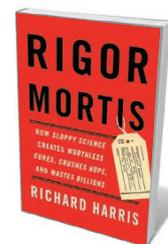


METASCIENCE

Reproducibility blues

Marcus Munafò enjoys a stinging survey of unreliable findings in biomedical research.



Rigor Mortis: How Sloppy Science Creates Worthless Cures, Crushes Hope, and Wastes Billions
RICHARD F. HARRIS
Basic: 2017.

The scale of the problem is laid bare: apparently trivial methodological differences (such as how cells are stirred in culture, or the medium on which they're grown) can mean a complete failure to replicate results. Animal models often poorly predict results in humans; sample sizes can be too small to give reliable results; and some 12,000 studies may have used contaminated or misidentified cell lines. It is not just that the published research is unreliable — we may also be missing out on good drugs because poor preclinical data is an unreliable guide to whether to pursue human studies. The term “Eroom’s law” (the reverse of Moore’s law) has been coined to describe the worsening state of drug discovery. How much funding is wasted? Is the self-correcting nature of the scientific method functioning optimally? And, can we do better?

Harris introduces us to the growing field of metascience — the scientific study of science itself — and some of those working in it. These reproducibility firefighters are providing answers to such empirical questions, and identifying interventions. Robert Kaplan and Veronica Irvin at the US National Institutes of Health (NIH) showed that when the National Heart, Lung, and Blood Institute required preregistration of primary outcomes (the main outcome against which success should be judged) in clinical trials, the proportion of studies reporting a benefit fell from 57% to 8%.

Failure is a normal part of science, but dressing it up as success (for example, by presenting a secondary outcome as the primary outcome) is misleading. So is packaging exploratory, hypothesis-generating work as confirmatory, hypothesis-testing work. Unfortunately, with few ways to publish negative results, such practices are encouraged by incentives to present clean results with a compelling narrative, and be the first to do so.

Unsurprisingly, views differ on the reproducibility ‘crisis’. Some believe we are in the dark ages; others, that attempts at direct replication are naive. The truth is probably in ▶

priceless collection of minerals and jewels, mostly by charming wealthy patrons, but bones beat baubles in my book.

Like my own *Dry Store Room No. 1* (Harper, 2008), based on my decades as a palaeontologist at London’s Natural History Museum (NHM), *Curators* is both an autobiography and a hymn to some of Grande’s more remarkable predecessors and colleagues. He is generous in their praise. Each year, he attends the Alabama Deep Sea Fishing Rodeo on Dauphin Island, where anglers give scientists first dibs on species that will contribute to the understanding of fish evolution. He secures important specimens — including a 175-kilogram Warsaw grouper (*Epinephelus nigritus*) — and fosters the prospects of his students by involving them in collaborative research projects.

I have shared several colleagues with Grande: Colin Patterson from my place, who is one of the founding fathers of phylogenetics, the study of evolutionary relationships; the amiable ichthyologist William Bemis; and Grande’s own teacher, the determinedly eccentric Robert Sloan.

What is missing is the life of the curator between adventures. The job does entail a lot of rifling around in drawers, discovering tiny details, consulting rare books and even writing labels. I love fieldwork, but it rarely takes up more than 10% of my time; laboratory work and often rather dry scholarly research account for the rest. Some museum curators rarely

“Far from the popular image of introverted specialists tending drawers deep in the vaults, the Field’s curators are Indiana Jones figures.”

venture into the field at all. And even Grande’s account loses immediacy as soon as he steps into the role of administrator.

Sadly, the importance of science centred on museum collections is losing traction. Fundraisers and public-relations people are replacing curators, even in national museums. At the NHM, the number of full-time fossil researchers has more than halved since the peak era of the 1970s. In some regional museums, curators are rarer than the specimens they study. This is tragic. Creeping philistinism values only the bottom line, and there is little money to be made in (say) fish evolution. Maybe Grande’s book will help to reverse the trend. ■

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As scientists, we are supposed to be objective and disinterested, careful sifters of evidence. The reality is messier. Our training can give us only so much protection from natural tendencies to see patterns in randomness, respond unconsciously to incentives, and argue forcefully in defence of our own positions, even in the face of mounting contrary evidence. In the competitive crucible of modern science, various perverse incentives conspire to undermine the scientific method, leading to a literature littered with unreliable findings.

This is the conclusion of *Rigor Mortis*, a wide-ranging critique of the modern biomedical research ecosystem by science journalist Richard Harris. He describes how a growing number of claims over the past decade that many published research findings are false, or at least not as robust as they should be, has led to calls for change, and the birth of a new discipline of metascience.

He begins with the revelation in 2012 by Glenn Begley that only 6 (11%) of 53 ‘landmark’ publications in preclinical cancer research could be confirmed by the biotechnology firm Amgen (C. G. Begley and L. M. Ellis *Nature* **483**, 531–533; 2012). Since then, numerous studies (most recently in psychology and cancer biology) have confirmed that failure to replicate published findings is the norm. The reasons are complex and contested. Harris identifies potential culprits, from the complexity of modern biomedical science to the limitations of tools and training, and perverse incentives in modern academia.



Mice are often poor models for human therapies.

▶ between, but the situation is sufficiently serious for key stakeholders to have begun to take notice and to introduce measures promoting robust design and transparent reporting. The NIH now has dedicated sections in grant proposals for applicants to describe how they will ensure their findings are robust, and *Nature* has introduced reporting checklists for submitted papers. There is growing interest in ‘open science’ — championed by the Center for Open Science in Charlottesville, Virginia — whereby elements of the research process (such as protocols, materials or data) are made publicly available. One positive outcome of the growth in meta-science is that it has highlighted how every field typically does something very well, from preregistration to data sharing.

It is ironic that scientists in the pharmaceutical industry — often the target of opprobrium and worries about conflicts of interest — were among the first to raise concerns about the functionality of biomedical science. But it isn't surprising. They have incentives to be right — to make a correct ‘go’ decision on a compound that proves to be a successful treatment. Academic scientists, by contrast, are incentivized to publish first, to get grants and so on, but only rarely to get the right answer. In the words of Veronique Kiermer, executive editor at the Public Library of Science in San Francisco, California, “It actually pays to be sloppy and just cut corners and get there first”. So what is good for scientists’ careers may not be good for science. Simulations support this, suggesting that labs that do sloppy science will ‘outperform’ more-rigorous ones.

Harris makes a strong case that the biomedical research culture is seriously in need of repair. His focus is on preclinical research (and is rather US-centric), but he ends on a more optimistic note. The culture in various branches of biomedical science is changing, and incorporating lessons from other branches — preregistration of protocols, reporting checklists, and open data and materials. There is also cross-pollination of ideas between academia and industry. And funders and journals have begun initiatives to improve the quality of research.

Looked at in this way, biomedical research is not in crisis, but is embracing an opportunity to improve how it works, using scientific tools to understand the scientific process. Change takes time; *Rigor Mortis* shows that reproducibility issues are now mainstream, and that can only be good for science. ■

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Pointing is an early milestone in children's communication.

LANGUAGE

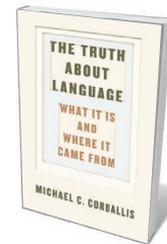
Points, grunts and speaks

Mark Pagel weighs up a study claiming that the origins of human language are rooted in gesture.

“Anyone can speak Troll. All you have to do is point and grunt.” Fred Weasley’s assertion in J. K. Rowling’s *Harry Potter and the Goblet of Fire* could describe the origins of human language. That is, if psychologist Michael Corballis is right in *The Truth about Language*. For years, Corballis has been one of the chief proponents of the idea that language has its origins in gestures. His latest book traces that argument from gesturing primates up through modern neuroscience.

Language is generally considered the jewel in the crown of human superiority over other animals. It seems to pop up almost out of nowhere in our evolutionary past, and no other animal’s communication comes close to it. Through clicks, hoots, barks, chirrups and bleats, some animals can inform each other of how they are feeling. And some, through gestures, can signal anger, impatience, dominance or submission, desire and attachment. But none can use these displays to convey a simple sentence such as “I kicked the ball”.

Being unique and powerful, human language is a siren to Darwinians, teasing us to examine how it arose, and from what. Corballis assigns a central role to the brain’s mirror neurons, which seem to echo action in observation (in monkeys, mirror neurons fire when they reach to grasp objects, and when they observe another animal doing the same). Corballis points out that there is an overlap between parts of the mirror-neuron system and two areas in the brain’s left cerebral cortex that are associated in humans with



The Truth about Language: What It Is and Where It Came From

MICHAEL C. CORBALLIS
University of Chicago Press: 2017.

the production and comprehension of language — Broca’s and Wernicke’s areas. Mirror neurons have their detractors (see P. Smith Churchland *Nature* 511, 532–533; 2014), but for Corballis they raise the possibility that language “evolved within a system that, back in our monkey days, was specialised for grasping things”. In humans, mirror neurons also seem to be involved with other actions. One is pointing. Conveniently for Corballis, this is one of the earliest milestones of communication in children (‘look at that’, ‘please get that for me’), emerging around the first year, and signifying the beginning of shared attention. It is also disrupted in social disorders, such as autism. And the fine control of facial muscles required for speaking seems to share cortical circuitry with regions that control gestures.

Still, what is wrong with the view that our language grew from our hominid ancestors’ capacity for vocalization? This was Charles Darwin’s favourite explanation, put forth in *The Descent of Man* (1871). He thought that the capacity for complex vocal learning had deep evolutionary roots, extending at least as far back as our common ancestor with birds. Corballis counters that primate vocalizations,