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PLoS CLINICAL TRIALS

Essay

Evolution and Translation of Research Findings: From Bench to Where?

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Summary

The credibility and replication of research findings evolve over time, as data accumulate. However, translation of postulated research promises to real-life biomedical applications is uncommon. In some fields of research, we may observe diminishing effects for the strength of research findings and rapid alternations of exaggerated claims and extreme contradictions—the "Proteus Phenomenon." While these phenomena are probably more prominent in the basic sciences, similar manifestations have been documented even in clinical trials and they may undermine the credibility of clinical research. Significance-chasing bias may be in part responsible, but the greatest threat may come from the poor relevance and scientific rationale and thus low pre-study odds of success of research efforts. Given that we currently have too many research findings, often with low credibility, replication and rigorous evaluation become as important as or even more important than discovery. Credibility, replication, and translation are all desirable properties of research findings, but are only modestly correlated. In this essay, I discuss some of the evidence (or lack thereof) for the process of evolution and translation of research findings, with emphasis on the biomedical sciences.

Translation of Basic and Preclinical Science

Translation of biomedical research findings to useful applications is a major challenge [1]. Thirty years ago, Comroe and Dripps [2] proposed that medical progress depends on basic research, but their methods and conclusions have been challenged [3,4]. Regardless, successful translation of research promises is uncommon. Among 101 articles published between 1979–1983 in six top basic science journals that clearly made promises for a major clinical application of their findings in therapeutic or preventive interventions, only 27 technologies were evaluated in a published randomized controlled trial (RCT) by 2003 [5]. Nineteen technologies were evaluated in at least one RCT with "positive" results, but only five of them are currently in licensed clinical use and only one is in wide clinical use today. Involvement of industry authors in the original basic science report and industry support increased translation to human experimentation 10- and 3-fold respectively.

Another study has examined [6] whether the results obtained in animal models of acute stroke guide the selection of agents for testing in humans. Across 1,026 agents tested in animals, the agents proceeding to human testing showed similar reductions in infarct size in animals as those that did not advance further. Thus selection for further translation did not seem to be guided by rational principles.

Other investigations have examined whether in vitro or in vivo biological research agrees with evidence on human participants on the same topic. One evaluation [7] of genetic polymorphisms showed no correlation between epidemiological odds ratios for disease susceptibility and in vitro effects on gene transcription in cell lines. Two other investigations addressed the concordance of epidemiological associations versus evolutionary conservation and tissue-based assays for genetic variants [8,9]. Despite some concordance, correlation was still modest.

The methodological quality of basic research is also largely understudied and there are only preliminary efforts to improve the reporting of basic and preclinical studies [10]. Rapidly evolving methods and technology are difficult to standardize. Nevertheless, animal studies with higher quality "scores" apparently find more precise and more conservative results than studies with lower "scores" [11,12]. Similarly, effect sizes appear larger in studies lacking randomization or blinding [13].

Some of the translation failure may be due to difficulties in communication between different fields in the spectrum of basic, preclinical, and applied research. Evidence-based medicine does not seem to have penetrated basic and preclinical science, while basic and preclinical research is often performed in a clinical and methodological vacuum (see Box 1).

Diminishing Effects and the Proteus Phenomenon

Replication of research findings in different studies means that, allowing for random fluctuation in early investigations, accumulation of evidence from many studies should converge towards stable estimates that don't shift with additional data [14]. However, sometimes we see continuously diminishing effects over time. Even large effects, and prominent claims, may gradually disappear [15–17] as more data accumulate (Box 2) [18–21].

In the "Proteus phenomenon," the first published study on a scientific question may find a most extravagant effect size; this is followed by the publication of another study that shows a large contradicting effect. Subsequent studies report effect sizes between these extremes [22]. Impressive findings have priority for publication. Strongly contradictory results may also have priority over replications and inconclusive results. The

Funding: The author received no specific funding for this article. This article extends on material presented at an invited talk given at the Society of Clinical Trials annual meeting, Orlando, Florida, in May 2006.

Competing Interests: The author has declared that no competing interests exist.

Citation: Ioannidis JPA (2006) Evolution and translation of research findings: From bench to where? PLoS Clin Trials 1(7): e36. doi:10.1371/journal.pctr.0010036

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Abbreviations: RCT, randomized controlled trial

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