

EDITOR'S CHOICE

How predictive and productive is animal research?

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It's more than 20 years since Doug Altman wrote his scorching editorial in *The BMJ* on "the scandal of medical research" (doi:10.1136/bmj.308.6924.283). Earlier this year *The BMJ*'s former editor Richard Smith summarised why the same editorial could be published today with little change (<http://bit.ly/1rHnWbL>), referencing the recent *Lancet* series on waste in medical research and John Ioannidis's *PLoS Medicine* article entitled, "Why most published research findings are false." The medical literature remains beset with academic and commercial biases caused by overinterpretation of small, poorly designed, and badly implemented studies, many of them erroneously or selectively reported or not reported at all. The result is an evidence base that systematically exaggerates the benefits and underplays the harms of treatments.

But as if this were not enough, an even more fundamental problem casts doubt on the validity of clinical research: the poor quality of the animal research on which much of it is based. Ten years ago in *The BMJ* Pandora Pound and colleagues asked, "Where is the evidence that animal research benefits humans?" (doi:10.1136/bmj.328.7438.514). Their conclusions were not encouraging. Much animal research into potential treatments for humans was wasted, they said, because it was poorly conducted and not evaluated through systematic reviews.

Since then, as Pound and Michael Bracken explain this week (doi:10.1136/bmj.g3387), the number of systematic reviews of animal studies has increased substantially, but this has served only to highlight the poor quality of much preclinical animal research. The same threats to internal and external validity that beset clinical research are found in abundance in animal studies: lack of randomisation, blinding, and allocation concealment; selective analysis; and reporting and publication bias. The result,

said Ioannidis in 2012, is that it is "nearly impossible to rely on most animal data to predict whether or not an intervention will have a favourable clinical benefit-risk ratio in human subjects."

Such wastage is as unethical in animal as in human research. Poorly done preclinical research may lead to expensive but fruitless clinical trials exposing participants to harmful drugs. And of course there is the unnecessary suffering of the animals involved in research that brings no benefit.

What to do about it? Better conduct and reporting of animal research will help, say Pound and Bracken. This could come from better training and education of basic researchers and from a cultural change fuelled by greater scrutiny and public accountability. But how much would this really improve the rate of successful translation from animals to humans? Not much, it seems. Even if the research were conducted faultlessly, argue the authors, our ability to predict human responses from animal models will be limited by interspecies differences in molecular and metabolic pathways.

Funds might be better directed towards clinical rather than basic research, where there is a clearer return on investment in terms of effects on patient care. The authors conclude: "If research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public's continuing endorsement and funding of preclinical animal research seems misplaced." Where would you place the balance of effort: investment in better animal research or a shift in funding to more clinical research?

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