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# Why animal studies are often poor predictors of human reactions to exposure

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The concept that animal research, particularly that relating to pharmaceuticals and environmental agents, may be a poor predictor of human experience is not new. A thousand years ago, Ibn Sina commented on the need to study humans rather than animals,<sup>1</sup> and Alexander Pope's dictum 'The proper study of mankind is man' is well known and has been widely cited.<sup>2</sup> Pharmacologists, in particular, have long recognized the difficulties inherent in extrapolating drug data from animals to man.<sup>3,4</sup> Given the large number of animal studies conducted, it would be expected that some animal experiments do predict human reactions. For example, penicillin was observed to protect both mice and humans from staphylococcal infections,<sup>5</sup> and isotretinoin ('Acutane') causes birth defects in rabbits and monkeys as well as in humans (although not in mice or rats).<sup>6</sup> By contrast, corticosteroids are widely teratogenic in animals but not in humans,<sup>7</sup> and thalidomide is not a teratogen in many animal species but it is in humans.<sup>8</sup> Recent experience in a phase 1 study of the monoclonal antibody TGN 1412 resulted in life-threatening morbidity in all six healthy volunteers, reflecting inadequate prediction even in non-human primates of the human response.<sup>9</sup>

One reason why animal experiments often do not translate into replications in human trials<sup>10,11</sup> or into cancer chemoprevention<sup>12-14</sup> is that many animal experiments are poorly designed, conducted and analysed. Another possible contribution to failure to replicate the results of animal research in humans is that reviews and summaries of evidence from animal research are methodologically inadequate.<sup>15</sup> In one survey, only 1/10,000 Medline records of animal studies were tagged as being meta-analyses compared with 1/1000 human studies.<sup>16</sup> In recent reports, the poor quality of research synthesis was

documented by a comprehensive search of Medline which found only 25 systematic reviews of animal research.<sup>17</sup> Other recent studies similarly found only 30<sup>15</sup> and 57<sup>18</sup> systematic reviews of any type of animal research. These deficiencies are important because animal research often provides the rationale for hypotheses studied by epidemiologists and clinical researchers.

The paper by Perel and his colleagues<sup>19</sup> has been added to the James Lind Library because it has made an important methodological contribution to understanding why animal studies may not predict human reactions. The authors conducted systematic reviews of the animal research relevant to studies in humans in six areas of research where confident estimates of intervention effects (benefit or harm) have been demonstrated in systematic reviews of randomized trials. The interventions studied were: corticosteroids for head injury; anti-fibrinolytics to reduce bleeding; tissue plasminogen activator to reduce death and disability after stroke; tirilazad for ischaemic stroke; antenatal corticosteroids to reduce lung morbidity and death in preterm newborns; and bisphosphonates to increase bone mineral density. In three of the research areas the animal studies and human trials were substantially discordant; in three others the results were essentially similar. In all areas of research, however, major methodological limitations of the animal research and evidence of widespread publication bias were identified.

Systematic review of animal studies is most advanced in the field of stroke research,<sup>20,21</sup> an area where almost no new human drug therapies have been developed despite decades of research. In one systematic review of FK506, for which 29 animal studies were found, only one study had blinded investigators to the intervention and only two blinded

observers during outcome assessment. None of the 29 studies met all 10 quality criteria applied by the reviewers (one study met no criteria; the highest score was 7). Meta-analysis of the studies demonstrated a strong trend for the methodologically weakest studies to show the strongest protective effects, and the methodologically strongest studies to show either no or weak protective effects.<sup>22</sup>

The few systematic reviews of the animal literature that have been done also pointed to the poor quality of other animal research, and the difficulty of extrapolating from it to humans,<sup>23</sup> a concern which is being increasingly made in other fields of drug development and evaluation.<sup>24,25</sup> Mathews<sup>26</sup> has recently challenged those who have claimed that 'virtually every medical achievement of the last century has depended directly or indirectly on research with animals' to provide evidence justifying their assertion.

Some of the key problems have been summarized by Pound and her colleagues<sup>17</sup>:

- Disparate animal species and strains, with a variety of metabolic pathways and drug metabolites, leading to variation in efficacy and toxicity;
- Different models for inducing illness or injury, with varying similarity to the human condition;
- Variations in drug dosing schedules and regimens of uncertain relevance to the human condition;
- Variability in animals for study, methods of randomization, choice of comparison therapy (none, placebo, vehicle);
- Small experimental groups with inadequate statistical power; simple statistical analyses that do not account for confounding; and failure to follow intention-to-treat principles;
- Nuances in laboratory technique that may influence results, for example, methods for blinding investigators, being neither recognized nor reported;
- Selection of outcome measures, which being surrogates or precursors of disease, are of uncertain relevance to the human clinical condition;
- Variable duration of follow-up, which may not correspond to disease latency in humans.

As Perel and his colleagues<sup>19</sup> and others referred to in this commentary have shown, animal studies will only become more valid predictors of

human reactions to exposures and treatments if there is substantial improvement in both their scientific methods as well as in more systematic review of the animal literature as it evolves. Systematic reviews of animal research, if they are used to inform the design of clinical trials, particularly with respect to appropriate drug dose, timing and other crucial aspects of the drug regimen, will further improve the predictability of animal research in human clinical trials.

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