Young people have the right to evidence based interventions. We know from the past that many well meaning attempts to do good resulted in harm, but we now have the means through systematic review, trials, sound evaluations, and good qualitative work, to do better.

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Where is the evidence that animal research benefits humans?

Pandora Pound, Shah Ebrahim, Peter Sandercock, Michael B Bracken, Ian Roberts on behalf of the Reviewing Animal Trials Systematically (RATS) Group

Much animal research into potential treatments for humans is wasted because it is poorly conducted and not evaluated through systematic reviews

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Clinicians and the public often consider it axiomatic that animal research has contributed to the treatment of human disease, yet little evidence is available to support this view. Few methods exist for evaluating the clinical relevance or importance of basic animal research, and so its clinical (as distinct from scientific) contribution remains uncertain.[1] Anecdotal evidence or unsupported claims are often used as justification—for example, statements that the need for animal research is "self evident"[2] or that "Animal experimentation is a valuable research method which has proved itself over time."[3] Such statements are an inadequate form of evidence for such a controversial area of research. We argue that systematic reviews of existing and future research are needed.

Assessing animal research

Despite the lack of systematic evidence for its effectiveness, basic animal research in the United Kingdom receives much more funding than clinical research.[1 4 5] Given this, and because the public accepts animal research only on the assumption that it benefits humans,[6] the clinical relevance of animal experiments needs urgent clarification.

Several methods are available to evaluate animal research. These include historical analysis,[7] critiques of animal models,[8] investigations into the development of treatments,[5] surveys of clinicians' views,[9] and citation analyses.[10] However, perhaps the best way of producing evidence about the value of animal research is to conduct systematic reviews of animal studies and, where possible, compare the results of these with the results of the corresponding clinical trials. So what do studies that have done this show?

Details of the search strategy and references w1-w18 are on bmj.com

Systematic reviews of animal research

We searched Medline to identify published systematic reviews of animal experiments (see bmj.com for the search strategy). The search identified 277 possible papers, of which 22 were reports of systematic reviews. We are also aware of one recently published study and two unpublished studies, bringing the total to 25. Three further studies are in progress (M Macleod, personal communication).

Seven of the 25 papers were systematic reviews of animal studies that had been conducted to find out how the animal research had informed the clinical research. Two of these reported on the same group of studies, giving six reviews in this category. A further 10 papers were systematic reviews of animal studies conducted to assess the evidence for proceeding to clinical trials or to establish an evidence base.[w1-w10] Eight systematically reviewed both the animal and human studies in a particular field, again before clinical trials had taken place.[w11-w18] We focus on the six studies in the first category because these shed the most light on the contribution that animal research makes to clinical medicine.

Calcium channel blockers for stroke

The first systematic review of animal research, by Horn and colleagues,[11] was conducted after their systematic review of clinical trials of nimodipine for acute stroke found no evidence of a clinically important effect.[12] Their review of the animal experiments with nimodipine found no convincing evidence of benefit to support the decision to start clinical trials. Horn et al also found that the methodological quality of the animal studies included in the review was poor, commenting on the infrequency of randomisation of animals, lack of blinded assessment, and failure to measure outcomes beyond the acute phase. Furthermore, the animal and clinical studies of nimodipine ran simultaneously rather than sequentially, as would be expected if the animal experiments were to inform the human trials.

Low level laser therapy for wound healing

Lucas et al investigated the basis for clinical trials of low level laser therapy to improve wound healing after the treatment was found ineffective in humans.[13] The authors found that the animal studies did not provide unequivocal evidence to substantiate the decision to conduct clinical trials, that the methodological quality of the animal studies was poor, and that animal and clinical studies were conducted simultaneously rather than sequentially. They commented on the relevance of the animal models to the real clinical situations, noting that the animal models excluded common problems associated with wound healing in humans such as ischaemia, infection, and necrotic debris.

Fluid resuscitation for bleeding

Roberts et al[14] and Mapstone et al[15] assessed the animal evidence in support of fluid resuscitation for bleeding trauma patients. Their systematic review of clinical trials of fluid resuscitation had previously found no evidence that the practice improved outcome and the possibility that it might be harmful.[16] The review of animal research found that the fluid resuscitation reduced the risk of death in animal models of severe haemorrhage but increased the risk of death in those with less severe haemorrhage. They concluded that excessive fluid resuscitation in animals can be harmful in some situations.

The review again highlighted the poor methodological quality of individual animal studies. Moreover, because the animal experiments were small, the effect estimates from these studies were imprecise. The authors argued that systematic reviews and meta-analyses of previous animal experiments would ensure that new animal experiments do not set out to answer questions that have already been answered and, by increasing the precision of estimates of treatment effects, could reduce the number of animals needed in future experiments.

Thrombolysis for stroke

An unpublished study by Ciccone and Candelise systematically reviewed randomised controlled experiments of animal stroke models that compared the effects of thrombolytic drugs with placebo or open control.[17] The background to the study was the finding that clinical trials of thrombolysis for acute stroke had found a substantial excess risk of intracranial haemorrhage that had not been predicted by individual animal studies. When the animal data were pooled, a significant difference was found in the rate of intracranial haemorrhage between animals in the control and treatment groups.

Stress and coronary heart disease

Petticrew and Davey Smith examined randomised and observational studies of the effects of hierarchies and stress on coronary heart disease in primates.[18] They found no convincing evidence of a relation between social status and experimentally induced stress and coronary heart disease. Among male primates, dominant rather than subordinate social position seemed to be associated with heart disease, contradicting a large body of observational epidemiological studies of stress and coronary heart disease.[19] The authors noted that social epidemiologists had cited only the studies that supported their prior views of a positive association and had ignored studies with negative results. Within psychosocial epidemiology, citation was highly selective, producing the misleading

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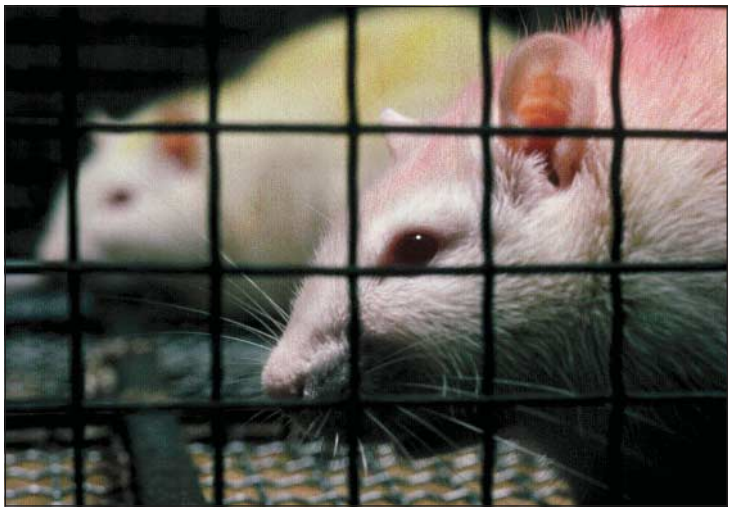

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The validity of animal research needs investigation

impression that primate studies support the view that the health effects of inequality are manifest through psychosocial mechanisms. The authors concluded that the primate data do not support such major public health claims.

Endothelin receptor blockade in heart failure

Lee and colleagues[20] conducted a systematic review and meta-analysis of controlled trials of endothelin receptor blockade in animal models of heart failure, after clinical trials in humans had found no evidence of benefit. They found that the animal studies were small and poorly designed with inconsistent use of randomisation and blinding. Pooled analyses of the animal data provided no evidence of benefit overall and showed a tendency towards increased mortality with early administration. The authors called for greater use of systematic reviews in preclinical drug evaluation.

Implications

The clinical trials of nimodipine and low level laser therapy were conducted concurrently with the animal studies, while the clinical trials of fluid resuscitation, thrombolytic therapy, and endothelin receptor blockade went ahead despite evidence of harm from the animal studies. This suggests that the animal data were regarded as irrelevant, calling into question why the studies were done in the first place and seriously undermining the principle that animal experiments are necessary to inform clinical medicine.

Furthermore, many of the existing animal experiments were poorly designed. Animal experiments can inform decisions about what treatments should be taken forward in clinical trials only if their results are valid and precise and if the animal studies are conducted before clinical trials are started. Biased or imprecise results from animal experiments may result in the testing of biologically inert or even harmful substances in clinical trials, thus exposing patients to unnecessary risk and wasting scarce research funds. Moreover, if animal experiments fail to inform medical research, or if the quality of the experiments is so poor as to render the findings inconclusive, the research will have been conducted unnecessarily. Investigating the validity of animal experiments is therefore essential for both human health and animals.

Although randomisation and blinding are accepted as standard in clinical trials, no such standards exist for animal studies.[21] Bebarta et al found that animal studies that did not report randomisation and blinding were more likely to report a treatment effect than studies that used these methods.[21] The box summarises further potential methodological problems.

Even if animal experiments provide valid results and sufficiently precise estimates of treatment effects to discount the effects of chance, the extent to which the results can reasonably be generalised to humans remains open to question. Perhaps it was because of this uncertainty that the data from animal studies were disregarded in the above cases.

Methodological problems of animal experiments

- 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 regimen that are of uncertain relevance to the human condition
- Variability in the way animals are selected for study, methods of randomisation, choice of comparison therapy (none, placebo, vehicle), and reporting of loss to follow up
- Small experimental groups with inadequate power, simplistic statistical analysis that does not account for potential confounding, and failure to follow intention to treat principles
- Nuances in laboratory technique that may influence results may be neither recognised nor reported—eg methods for blinding investigators
- Selection of a variety of outcome measures, which may be disease surrogates or precursors and which are of uncertain relevance to the human clinical condition
- Length of follow up before determination of disease outcome varies and may not correspond to disease latency in humans

Conclusion

The contribution of animal studies to clinical medicine requires urgent formal evaluation. Systematic reviews and meta-analyses of the existing animal experiments would represent an important step forward in this process. Systematic reviews (particularly cumulative meta-analyses of ongoing experiments[22]) could more efficiently determine when a valid conclusion has been reached from the animal studies. The UK Medical Research Council requires researchers who are planning clinical trials to reference systematic reviews of previous related work.[23] A requirement to reference, or where necessary conduct, systematic reviews of relevant animal studies before clinical trials would make it difficult to disregard or selectively cite the evidence from animal studies, or for animal and human trials to proceed simultaneously.

By ensuring that animal experiments do not set out to answer questions that have already been answered, systematic reviews support the principle of reduction. This principle, outlined in the "three Rs," (reduction and replacement of animals and refinement of procedures), is held to be a cornerstone of animal research.[24] Systematic reviews would also be relevant in veterinary medicine to evaluate the efficacy of treatments for sick animals.

Systematic reviews of animal research would increase the precision of estimated treatment effects used in calculating the power of proposed human trials, reducing risk of false negative results. They are able to throw light on the process of translation (or its lack) between animal and clinical research as well offering the opportunity to review the appropriateness of the animal models used. Finally, the results of the animal and human research need to be compared to see how well one predicts the other.

In the 1970s Comroe and Dripps conducted an ambitious study to determine the relative contributions of basic and clinical research to important medical

Summary points

- The value of animal research into potential human treatments needs urgent rigorous evaluation
- Systematic reviews can provide important insights into the validity of animal research
- The few existing reviews have highlighted deficiencies such as animal and clinical trials being conducted simultaneously
- Many animal studies were of poor methodological quality
- Systematic reviews should become routine to ensure the best use of existing animal data as well as improve the estimates of effect from animal experiments

advances.[25] They concluded that 62% of key articles that led to advances were the result of basic research. In the 1980s Smith highlighted many of the methodological shortcomings of Comroe and Dripps' study.[26] He concluded that the study was unscientific but that the main lesson to be gained is that research itself needs to be researched so that scarce funds can be allotted more intelligently rather than on the basis of anecdotal evidence. More recently, Grant et al noted that Research Council expenditure on basic research increased in the United Kingdom from 42% of the total civil research and development in 1991-2 to 61% in 1998-9.[5] While recognising that it would be difficult to attribute this increase to the work of Comroe and Dripps, they observe that their study is often quoted in support of increased funding for basic biomedical research. Grant et al attempted to replicate the Comroe and Dripps study and found that it was "not repeatable, reliable, or valid and thus is an insufficient evidence base for increased expenditure on basic biomedical research."[5]

The Cochrane and Campbell Collaborations for systematically reviewing evidence in health care and social science offer models for how the literature on animal experiments might be systematically organised and examined.[27 28] Several sources of potential bias exist in systematic reviews—for example, pharmaceutical industry animal trials are likely to be excluded from the public domain for commercial reasons, resulting in publication bias in systematic reviews—but space precludes considering them here. Ideally, new animal studies should not be conducted until the best use has been made of existing animal studies and until their validity and generalisability to clinical medicine has been assessed.

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Contributors: The authors include one sociologist and four epidemiologists, three of whom conduct systematic reviews for the Cochrane Collaboration. The ideas in this paper have developed through our involvement in conducting systematic reviews and clinical trials, in reviewing animal studies before trials, and in examining the reasons behind our failure to find successful treatments for stroke and brain injury.

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