human errors can be made irrelevant to outcome, continually found, and skilfully mitigated. So long as it involves humans—and thank God it does—health care will never be free of errors. But it can be free of injury.

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Animal research: the need for a middle ground

Let's promote the three Rs of animal research: replacement, reduction, and refinement

Many countries, including Britain, suffer from grossly oversimplified debates on important issues like drugs, crime and punishment, genetically modified foods, and animal research. Are you for or against? Sign here. Yet none of these issues is moved forward by such polarised arguments. The British debate on animal research currently features people in balaclavas using every tactic, including illegal and violent ones, to close down animal research institutes pitted against intimidated scientists arguing that no progress can be made in treating serious human diseases without animal research. We need more understanding of the complexities of animal research and a greater concentration on where we agree.

Can any of us imagine a world where animals were not used for food, clothing, or transport, where we had no pets, where rats and other vermin were not controlled, and where an ape, or even a fly, was regarded as the moral equal of the Archbishop of Canterbury? Most of us can't, and many people in Britain accept the need for some animal research.[1] Yet most of us would not tolerate a world where animals had no rights and could be exploited for whatever cause. We thus have to find some middle ground in our relationship with animals, and a world that tries to afford more rights to men and women will probably also try to give more to animals.

The arguments over animal research are so polarised because the two sides have completely different ways of thinking.[2] Opponents of research are concerned primarily with the rights and suffering of animals, whereas supporters are interested in the capacity of animal research to speed developments in understanding biology and preventing and treating disease. We need methods and ideas to promote agreement rather than disagreement, and the three Rs of animal research—replacement, reduction, and refinement—can do just that. They were first proposed by William Russell (zoologist, psychologist, and classical scholar) and Rex Burch (microbiologist) in 1959.[3] Replacement is "any scientific method employing non-sentient material which may … replace methods which use conscious, living vertebrates." Reduction is lowering "the number of animals needed to obtain information of a given account and precision." Refinement is any development that leads to a "decrease in the incidence or severity of inhumane procedures applied to those animals which have to be used."

The three Rs underpin most animal research policy and practice. They start with the assumption that there will be animal research but hold open the possibility that science might advance to a point where it would no longer be necessary. Replacement is the option that is most attractive to animals lovers and politicians and has been actively promoted by the Fund for Replacement of Animals in Medical Experimentation (www.frame-uk.demon.co.uk) and the European Centre for the Validation of Alternative Methods, which was set up by the European Union.[4 5] Replacement can be relative (using humane killing to provide cells, tissues, or organs), absolute (using permanent cultures of cells or tissues), direct (using, for example, skin in vitro rather than in vivo), indirect (replacing, for example, the pyrogen test in rabbits with a test on whole human blood), total (using a human volunteer), or partial (using non-animal methods in prescreening of toxic compounds).[2]

The science of replacement is growing rapidly, but the Holy Grail of complete replacement of animals is as far off as ever.[2] The central problem is that molecular, cell, tissue, or organ models are highly simplified when compared with whole animals or humans. After 20 years of research there are only a handful of validated and genuine replacements for animal methods.

Reduction has not received the same attention as replacement, and seems to be still more difficult.[6] It depends primarily on better research and better statistical analysis, which will be brought about through improved education and training. Reduction can also compete with refinement in that using fewer animals to achieve the same level of precision might mean exposing animals to greater suffering. Nevertheless, the number of animals used in scientific procedures in Great Britain has fallen over the past 20 years. In 1998, 2.66 million procedures were carried out—a reduction of more than 25% since the introduction of the Animals (Scientific Procedures) Act in 1986.[7]

Refinement has also been neglected relative to replacement, but the notion has been broadened to include all aspects of the life of a laboratory animal—from birth to death. Researchers worry that refinement may make the science less sound (so possibly rendering the animal's suffering worthless), but a joint working group of the Royal Society for the Prevention of Cruelty to Animals, FRAME, the Universities Federation for Animal Welfare, and the British Veterinary Association Animal Welfare Foundation have made specific recommendations for advancing refinement.[8]

The beauty of the three Rs is that they provide a way for all parties to work together to advance the cause of both animals and humans. Nothing will be gained by forcing laboratories to close or by oversimplifying the debate. Lesley Grayson (whose

BMJ 2001;322:248–9

work I've quoted liberally) has made a huge contribution to this important debate by producing for the British Library a summary of important papers and reports on animal research from all relevant disciplines. She concludes: "I began work on this book, knowing relatively little about the issues and thus, as someone of rational disposition, with no very marked tendency towards any of the major camps in the debate. I end in much the same state of mind."

Richard Smith *editor, BMJ*

Competing interest: The *BMJ* hardly ever publishes animal research. This is not because we are against animal research but rather because we favour research that may have results that are directly applicable for clinicians and those making public policy. While doing a degree in experimental pathology in 1973 I implanted stem cell leukaemias into rats. I wrote this editorial a few days after our pet rabbit was killed by a fox. Her death upset me much more than I ever expected.

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Insecticide treated bed nets to prevent malaria

The challenge lies in implementation

Papers p 270

Evidence of the impact of insecticide treated materials, either bed nets or curtains, on morbidity from malaria and mortality from all causes in children has been growing over the past 10-20 years.[1 2] The studies have been carried out mainly, although not exclusively, in Africa (11 clinical trials out of 18 in the Cochrane review), the continent where 80% of all clinical cases and over 90% of all malaria deaths are estimated to occur. These data provide strong evidence that insecticide treated materials can substantially reduce childhood mortality, at least in places where malaria is a major contributor to death. However, all these trials were carried out in a way impossible to reproduce on a large scale and they measured efficacy—the potential impact of insecticide treated materials when implemented in almost ideal conditions. Problems can arise when bed nets are promoted outside the context of a clinical trial—though a paper in this week's *BMJ* (p 270) also suggests an approach that might circumvent some of them.[3]

The impact of insecticide treated materials on mortality was determined by intervention studies carried out in four African countries.[4–7] All reported an impact on all cause childhood mortality, although this was not uniform (ranging from 15% to 63%) and fell with increasing intensity of malaria transmission. However, when the risk difference was used the insecticide treated materials seem to work at least as well in areas of high endemicity as in areas of lower endemicity.[8]

The first answer to the question of what impact insecticide treated materials would have outside of controlled trials came from the Gambia, where an epidemiological evaluation of the national insecticide treated bednet programme (NIBP) was undertaken. Bed nets are commonly used in the Gambia, and the national programme had the objective of treating with permethrin nets already in use in all large villages (400 people or more) over a two year period. During the first year insecticide was distributed free of charge, but in subsequent years a small fee was demanded. In the first year about 80% of existing nets were treated with insecticide, and a 25% decrease in all cause mortality was observed among children under 10.[9] However, the following year the introduction of the fee for the insecticide resulted in a drop in coverage (only 14%) and no impact on mortality.[10]

Here is a problem for the managers of malaria control programmes: the use of insecticide treated materials on a large scale can result in huge health benefits, and they are a cost effective intervention.[11] In many cases, however, the introduction of insecticide treated materials requires behavioural changes, particularly where the use of bed nets is low, so it is not always clear how these benefits can be obtained. Moreover, some form of cost recovery might have to be built into the programme—simply in order to sustain it—but this might have an important adverse influence on coverage. In particular, a policy of cost recovery will reduce access for poorer groups in the population. An apparently simple intervention thus becomes difficult to implement when the issues of coverage, accessibility, equity, and sustainability are considered. We need new approaches to tackle these issues.

Social marketing uses the methods of commercial marketing and applies them to a product with a social benefit. It has already been successfully used to promote the use of condoms, contraceptives, and oral rehydration solutions, and in this week's issue Abdulla et al describe its use for promoting insecticide treated bed nets in the Kilombero valley in Tanzania (p 000).[3] The results are impressive, not only because of the rapid increase of net ownership and the resulting high percentage of treated bed nets in just three years but also because of the dramatic impact on anaemia, parasitaemia, and splenomegaly in children aged under 2 years. This indicates that the social marketing programme succeeded in convincing the population of the usefulness of using insecticide treated materials, even though a payment had to be made.

The campaign described by Abdulla et al was carefully planned and used a pragmatic approach involving the public and private sectors.[12] Several points

BMJ 2001;322:249–50