The Second International Symposium on Infection Models in Antimicrobial Chemotherapy

We complete our publication of the selection of notes, chosen by the Editorial Board of CMI, based on reports from the Reykjavik meeting in July 1996.

Claude Carbon

Ethical considerations in the use of animal models in infection

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The use of animal models in the study of infectious diseases can make a valuable contribution to finding ways of treating human and animal diseases that occur in the world today. Such models will involve studying the processes involved in specific infections, as well as the development of vaccines and antimicrobial drugs, and measuring their effectiveness. Having said that, it must be ensured that the use of animals is essential and that appropriate models are used, and that other methods not involving animals cannot be used (in fact, very often both in vitro and in vivo methods are used, as they answer different questions).

Despite the fact that this use of animals provides useful and important information about many aspects of a disease and its cure, the public is still concerned at the ways in which animals are used in research. This reflects a general concern over animal welfare and is not confined to those used in research, but also includes, for example, farming, sport, wild animals, zoos and circuses [1]. There is a general view that it is wrong to cause animals pain and suffering, and so the deliberate infliction of suffering for no good purpose is described as 'cruelty' and is an offence in many countries. Animal research causes pain and suffering but it is considered acceptable because of the benefits that come from it. However, that does not mean that scientists can do anything to animals in the name of science. There are perhaps four crucial points to consider: the purpose of the experiment should be a good one with significant benefit; any animal suffering should be avoided or always be the minimum necessary to achieve the scientific objective; any animal suffering should be commensurate with the potential benefits; and it should be noted that there are strong scientific reasons to reduce animal suffering because the suffering itself may give rise to misleading research results which ultimately may result in more animals being used than necessary.

Avoidable animal suffering can occur as a result of poor husbandry, routine scientific procedures carried out incompetently (such as restraint, transport, injections), and poor experimental design. The resultant adverse physiologic and psychological responses of the animal will lead, amongst other things, to a release of corticosteroids which may well suppress the immune system, making animals less suitable for the research into infection, or even die. This only adds further unnecessary expense to the cost of research in terms of animals, scientists' time and consumables because of the misleading results. Furthermore, it is inhumane to cause avoidable suffering and to use more animals than necessary.

So does research into infection cause particular ethical problems and can the standards of animal research in this area be improved? A look at it from the animals' viewpoint, as opposed to the scientific viewpoint, may highlight some areas where improvements could be made with little or no financial cost, and with benefit to the science as well as to the animals. First, there are some general points to consider. Some models of infection are clearly better than others, and a model must do more than simply mimic the clinical signs of that disease in humans. Ideally, it should have the same pathogenesis as the human disease, the microorganism should infect and progress in a similar

manner, the immune response should be similar, and infection should result in similar sequelae and prognoses. As more becomes known about the genetic variability of humans and microorganisms, so it should be possible to devise better animal models and strategies for dealing with infectious (and non-infectious) diseases, e.g. using transgenic animals, gene knock-out animals, and genetically modified microorganisms.

Before work goes ahead, several other questions may be asked in order to ensure that humane research is being carried out. For example, is it possible to do the work in vitro; is the proposed model the best one available to answer the scientific question; can a less sentient species be used; are the facilities appropriate for the work and are there adequate staff to monitor the animals at critical times, e.g. when they are likely to die so that they can be humanely killed; is the experiment well designed; could more information be gained with a different design or statistical analysis; are pilot studies required, such as dose sighting; are the endpoints clearly defined, recognizable and humane, so that animals can be killed when they are no longer useful scientifically, or when the suffering is not justified by the potential benefit [2]. These sort of questions should be posed and advice taken before going ahead with the in vivo animal model. Russell and Burch [3] summed this approach up as the 'Three Rs': replacement, reduction and refinement. Respectively, these are: to replace animals with in vitro methods wherever possible; to use as few animals as possible (although it is just as wrong to use too few animals in research as it is to use too many, and so sound statistical advice should be sought); and to cause as little suffering as necessary to achieve the scientific objective, i.e. not to cause avoidable suffering.

Refinement comprises those methods which alleviate or minimize the potential pain, distress or other adverse effects suffered by the animals involved, or methods by which animal wellbeing can be enhanced, whilst retaining the scientific objective [4]. However, before one can start to refine an experiment, one has to be able to recognize when animals are suffering. Once animal suffering has been recognized, it becomes possible to assess it and to make changes in order to avoid, alleviate and reduce it.

At the University of Birmingham we are developing an assessment sheet recording system for measuring adverse effects on an animal during an experiment [5–7]. These sheets are specifically drawn up for each experimental model and for each species. Basically, the sheets record clinical signs observed over time. They encourage animal care-takers and researchers to recognize and assess signs of animal suffering such as pain, discomfort and distress. They provide a complete record of the effects of the scientific procedure on animals and encourage all involved in the research to observe the behavior of animals, and to recognize normal and abnormal behaviors. They help train new and old technicians by raising the awareness of all those involved in the experiment and they are especially useful with new procedures when users are not always sure of what effects they will have. Finally, the sheet can help to refine and to devise humane endpoints [8].

The European Experimental Infection Ethics Committee, under the Chairmanship of Professor Claude Carbon, was set up to start to look at determining best practice in various models of infection, i.e. to apply the Three Rs. The Committee has produced one model of best practice for endocarditis, and we hope to produce others in the near future.

In conclusion, I hope to have explained why it is important to refine animal experiments so that animal suffering is reduced to the minimum for reasons relating to humane and responsible science, as well as good science. Such an approach provides for an effective use of scarce research resources. It is also important that animal models are fully written up in scientific journals so that best practices can be disseminated to others working in the field [9,10].

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