Abstract

This report presents analysis by the Research Animals Department (RAD) of the RSPCA of information relating to xenotransplantation research on primates carried out by, and on behalf of, Imutran at Huntingdon Life Sciences (HLS). The information was contained in documents leaked to Uncaged Campaigns and placed on their website, together with 'Diaries of Despair' Uncaged Campaigns' own report on the material.

RAD staff carefully examined the leaked material and formed our own questions, concerns and conclusions before reading Diaries of Despair and comparing our points with those of Uncaged. We had access to additional material including: a document from Imutran responding to the Uncaged report; video footage of a baboon who had had transplant surgery; the report from the Chief Inspector of the Home Office of his investigation into the issue; and many relevant documents already in the public domain. The Head of RAD is a member of the Animal Procedures Committee (APC) and the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) so she was also aware of essential background information which was not publicly available. In addition, we had discussions with the Home Office Inspectorate and with HLS staff.

Throughout our analysis we endeavoured to make an objective assessment of the factual information available. We did not respond to assumptions or conjectures since this would have lessened the value of our report. The Uncaged report targeted its criticism specifically at HLS, Imutran and its xenotransplantation research programme, and at the Home Office as the regulatory body. RAD staff considered that the majority of the issues were widely applicable to the regulation of research in general, and should be reviewed in that context. It was this approach that resulted in Imutran agreeing to an exception to the injunction, allowing this report to be produced.

Organisation of the RAD report

The report is divided into two parts. **Part A** describes the context and terms of reference which we were allowed and our method of review. It sets out the terms of the injunction and (in section A2) the basis for the exemption granted to the RSPCA. The material that was available to RAD is described, together with the constraints imposed both by the incompleteness of this material and by the many layers of confidentiality. These constraints are inherent in carrying out an investigation based on this sort of material. Confidentiality under the Animals (Scientific Procedures) Act 1986 (ASPA), in particular, has seriously obstructed our efforts to find out exactly what happened to the animals involved. This has to be a major concern.

First, with respect to the leaked documents, these only present a 'snapshot' of Imutran's xenotransplantation research programme. Details of the research and matters such as how and why it was done, how the regulatory controls were applied, and the level of monitoring are very incomplete. Much of the material is labelled as 'draft' and the correspondence in general is fragmented, often with only parts of an exchange present. Even the 39 study reports, which are the most detailed documents, contain only limited information. This made it impossible for RAD to analyse fully

what happened to the animals involved and for what reason, or the levels of compliance with relevant legislation and Codes of Practice. A full investigation of this sort could only be carried out by the Home Office as the authority responsible for the administration of the ASPA. This was subsequently done by the Chief Home Office Inspector, who was charged by the Home Secretary with investigating the details of Imutran's compliance with the licence authorities issued under the ASPA. He had access to far more information than that available within the leaked documents, including information that would not normally be made available even to the Home Office (HO). The majority of this information remains confidential and cannot be divulged to the RSPCA.

The constraints imposed by confidentiality relate to: a) confidentiality under ASPA; b) confidentiality between government bodies such as the Home Office, APC and UKXIRA; and c) confidentiality due to the injunction. Thus, there are limits on the information to which a body such as the RSPCA is allowed access, and on the information that we are allowed to divulge. RAD staff have a high level of involvement and expertise in animal welfare and legislation controlling animal experiments, and our Head of Department is a member of both the APC and UKXIRA.

She has been granted access to relevant material and we have met with HLS staff and the Inspectorate to discuss the issues. As a result, many of our questions and concerns have been satisfactorily answered, but we are unable to place this information in the public domain. This means that throughout the report we have had to reiterate questions to which we know the answers because we believe these questions are important and require answering in the public domain. Furthermore, despite all the information we have seen, we still cannot say with any degree of confidence what proportion of the animals involved in this research experienced substantial levels of suffering, what was really done to alleviate the pain, suffering or distress experienced by any of them, or how the provisions of the ASPA were actually interpreted in practice. This situation has to be a cause for serious concern.

Part B of the report is our completed analysis of all the information available to us. The concerns and questions fall into three main categories:

(i) xenotransplantation as a technology and as an issue of public concern, including the way that scientific developments are reported in the public arena;

(ii) primate issues separate from their use in procedures including acquisition, transport, and husbandry;

(iii) compliance with, and implementation of, the ASPA.

These are addressed in Part B sections 2, 3 and 4-9 respectively. Some key points are set out below but it is important to refer to the full details in the main body of the text.

(i) Xenotransplantation as an issue of public concern

Xenotransplantation, both as a developing technology and because of the associated use of animals (and particularly primates) in experiments, are serious issues for the

public and animal protection organisations. The Department of Health Advisory Group on the ethics of xenotransplantation (the Kennedy Committee) stated in its 1996 report that the ethical acceptability of xenotransplantation depended on the full evaluation of its costs and benefits, and it emphasized that such assessments are not a 'one off' event. The 'costs' (harms) to animals both as sources of xenografts, and in particular in the associated research, are unquestionably extremely high. We do not believe that all of them, i.e. the summation of all the possible causes of pain, suffering or distress, have been fully appreciated in terms of understanding what the animals really experience. It is our view that, as a consequence, the costs have not been adequately taken in to account in the overall assessment of the ethical acceptability of xenotransplantation. (Note, this is outside of the specific cost/benefit assessment required under the ASPA). Furthermore, the anticipated benefits of the technology as applied to solid organs have not been realized. We therefore believe that a stringent and critical re-evaluation of xenotransplantation is long overdue.

In order to make informed decisions, as individuals and in the wider social and medical context, the public (and decision makers in general) need to understand the implications of the technology for all those involved in its development and/or application. This includes laboratory animals. It is thus imperative that detailed and meaningful information regarding the full impact of xenotransplantation research on the animals concerned should be easily accessible in the public domain, otherwise people cannot make a fully informed judgement on whether they believe the development of xenotransplantation is ethically acceptable. More open, honest and objective information, and reporting of this information, by the scientific community, industry (in this case specifically, Imutran and Novartis) and the media is also necessary. This must however apply to all interested parties including animal protection groups, something we have endeavoured to do in our report.

(ii) Primate issues

Primates are highly intelligent social animals who in the wild have large home ranges covering a rich and varied habitat in which they display a complex range of behaviours. Confining them in laboratories and using them in experiments, particularly of the sort reported here, causes a great deal of suffering which RAD considers to be unacceptable.

Under the ASPA, the use of primates requires special justification and the suffering of those used must be minimised. If either provision is to be properly addressed, then it is essential that all those involved with primate use are aware of <u>all</u> the stresses that research imposes on animals. In addition to the suffering associated with experiments, there are many concerns which relate to the acquisition, transport, husbandry and care of primates. These are illustrated by the information we reviewed. These concerns, and most of the information on which they are based, are not new and have been reported on previously by the RSPCA. Most of the information is already in the public domain and is covered in detail in the Society's latest report on the primate trade, *Counting the Cost* which makes substantive recommendations for action by those involved in regulating, and/or carrying out experimental procedures on animals.

The RSPCA believes the whole issue of primate acquisition and transport needs to be urgently re-evaluated and this view is reinforced by the material contained in the section of our report which deals with primate supply and transport. Our recommendations have already been set out in the *Counting the Cost* report and are thus not repeated here. They are aimed at preventing the specific problems illustrated in this report, although clearly, the Society's goal is to see an end to the transport and use of primates in experiments.

Questions and concerns about the level of suffering of the animals and the justification for their use are addressed in the section on the implementation of the ASPA.

(iii) Compliance with and implementation of ASPA

The Uncaged report focussed on issues of compliance with the ASPA; the investigation carried out by the Chief Home Office Inspector dealt only with compliance issues. However, compliance with legislation is not the only, or even the main consideration in our view, and we have identified a series of fundamental concerns with respect to the way the current regulatory system (against which compliance is assessed) operates, and this has formed the basis of this section of our report. We nevertheless agree with the majority of the Chief Inspector's conclusions and have had further discussions with the Inspectorate regarding these.

Our concerns are set out in detail in our report. They relate to matters including:

- assessment of the justification for animal use;
- prediction, assessment and weighing of harms and benefits – the factors that are taken into account, how this is done, and who by;
- levels of suffering and the relation between predicted and actual harms;
- amelioration of suffering;
- monitoring of animals;
- experimental end-points;
- animal husbandry;
- training of staff;
- ongoing and retrospective review;
- reporting to the HO and the APC;
- roles and relationships between the HO, APC and UKXIRA.

There are many over-arching questions about how decisions on all of these issues are made by those regulating and/or carrying out the research. We believe the answers to these questions belong in the public domain.

We believe that although this research was carried out at HLS, the primary responsibility for the concerns identified in our report lies with Imutran, because it is their research programme, carried out under their project licences for which they have responsibility. We believe that Imutran (now Novartis/Biopharma) should undertake a serious and critical review of its entire international research programme to significantly reduce its impact on animals of all species – even if this means abandoning some areas of research altogether. Where primates are concerned the company should obtain the input of those experienced in primate health, welfare and

behaviour to help properly assess the level of primate suffering. The company should also be prepared to openly acknowledge the suffering that their research imposes on primates and other animals.

Outside of this specific recommendation regarding Imutran there are a number of extremely important, although more general, points about the implementation of ASPA that we would like to draw attention to here.

The ASPA defines the basic provisions of the legislation; the associated Codes of Practice set out the standards of husbandry and care that must be applied. There is, however, a broad range of interpretations of what it is necessary to do to implement the ASPA in letter and in spirit, particularly with regard to those provisions that have a bearing on the justification for animal use, the application of the Three Rs of reduction, refinement and replacement, and animal husbandry and care. For example, it is widely recognised that the cost-benefit assessment that underpins the process by which licences are granted is, by its very nature, subjective. There is an inherent difficulty in weighing disparate factors such as the costs to individual animals of loss of life and suffering against potential benefits, but there are also many different interpretations of what actually counts as a cost in the first place. There are also different levels of recognition (in theory and in practice) that costs occur, and of how far it is possible or necessary to go to reduce or avoid them. Even where there are clearly defined requirements, such as for animal husbandry, there are problems. Thus, according to the information made available to the RSPCA, the standards at HLS complied with the Codes of Practice, and exceeded these in some respects. Our criticism is that these Codes of Practice are in themselves totally inadequate to meet the psychological and social needs of primates and many other species.

In summary, there are a range of standards and policies that are applied to: the most ethical and expedient research directions; the perceived need to proactively seek alternative approaches to avoid the use of animals and refinements to procedures; providing channels for progressing new information on the Three Rs; animal husbandry and care; and ensuring that everyone involved is empathetic, trained, competent and motivated continually to improve all of the above.

One person's good standards in any of these areas may be another's basic minimum. What one person finds acceptable – and that would be acceptable in law – can be unacceptable to another. These differences in opinion occur between people working under the ASPA, e.g. different NVSs, NACWOs or project licence holders within and between establishments; this is not just about the different views held by animal protectionists and scientists. There are also differing perceptions of what components of the regulatory system (including the HO Inspectorate, the APC, and UKXIRA) can or cannot do under the law, what their precise roles are, and how they actually operate, e.g. how licence applications are processed and monitored in practice by these authorities. It is vitally important for this to be more widely recognised and acknowledged and for the whole regulatory system to become far more open and transparent.

In conclusion

The questions we have posed throughout our report demand immediate, serious and thoughtful attention. They should not be the subject of yet another consultation exercise or left to a select committee examining generalities with regard to animal experimentation. They require focussed and critical analysis with the aim of informing future decision making, improving on current practice with regard to the use of animals under ASPA, and ensuring greater transparency with regard to the whole regulatory process.