Part A

The context and terms of reference of this report

1. Historical background

In September 2000 the organisation 'Uncaged Campaigns' released a report entitled Diaries of Despair which, it states: *"organises and interprets an extensive cache of leaked documents that afford an extraordinary and unique insight into arguably the most controversial programme of animal experimentation in the United Kingdom in modern times: xenotransplantation research"* [1] The report was based on the draft reports of 39 xenotransplantation studies carried out by the company Imutran at Huntingdon Life Sciences (HLS) together with other material including correspondence, minutes of Imutran meetings, internal reports, and feasibility studies concerning many aspects of the conduct of, and plans for, xenotransplantation research.

The report and the material on which it was based were distributed by Uncaged via the internet from which it was downloaded by the RSPCA. Some of the main points regarding the suffering of the animals used, criticism of the justification for the research and of the regulatory system controlling animal experiments in the UK, were reported by the Daily Express on September 21, 2000, in an article entitled "Terrible despair of animals cut up in the name of research" [2].

On September 26, Imutran's lawyers obtained a Court Order preventing the publication and distribution of the background material and the Diaries of Despair report on the grounds that the material (and hence the report) were drawn from a large body of documents that were confidential to the company and the copyright in which was owned by the company[3] Uncaged challenged this injunction but were unsuccessful and, at the time of writing this report, it is still in force pending a court hearing between Uncaged and Imutran.

The RSPCA, however, considered that the issues raised in the Diaries of Despair report were of sufficient concern to warrant immediate investigation[4]. The Society therefore applied to the Court for an 'exception' to allow it to review all the downloaded material and to prepare a report. A 13-page witness statement from Dr Maggy Jennings, Head of the Research Animals Department (RAD) at the RSPCA was submitted to support the Society's application[5]. This witness statement described the Society's concerns and the reasons that it believed a review was essential. The request was agreed by Imutran and granted at the Court hearing on 10 October 2000.

The injunction did not prohibit the supply of the documents or the information derived from them to various bodies concerned with the regulation of xenotransplantation research, or their use by those bodies in the course of their official functions. This included the Home Office (HO), the Animal Procedures Committee (APC) and the United Kingdom Interim Xenotransplantation Regulatory Authority (UKXIRA).

In early November 2001, Imutran prepared a report analysing and responding to the allegations made by Uncaged, which was made available on a confidential basis to the RSPCA and the relevant regulatory authorities.

The allegations made by Uncaged were subsequently raised in parliament as a parliamentary question to the Home Secretary[6]. In response, the Home Secretary said that he had asked the Chief Inspector of the Home Office to carry out a routine review of compliance with the relevant project licence authorities. In addition, he stated that the ad hoc Select Committee of the House of Lords set up to examine the use of animals in scientific experiments *"would provide an opportunity for the wider issues raised in the context of the Imutran case to be considered"*. The Chairman of the APC wrote to the Home Secretary on the Committee's behalf in January and March, 2001, expressing surprise at the decision not to instigate a special investigation or to carry out a retrospective review of the cost-benefit assessment (i.e. the justification) of the research[7].

The report from the Chief Inspector[8] became available just prior to the completion of this RSPCA report. Both the APC and UKXIRA have discussed the matter and intend to hold fuller discussions now that the Chief Inspector's review is available. In the case of the APC, specific issues will be addressed by the relevant sub-committees and working groups.

Imutran is owned by Novartis Pharma AG. The parent company announced in September 2000 that it was to join forces with Biotransplant Incorporated and move its research programmes to Boston USA[9]. This had been planned for some considerable time. The UK facilities were closed and the research described in the present report is therefore no longer carried out in the UK, although similar studies are being carried out by Novartis/Biotransplant and others in the international arena.

2. The terms of the RSPCA exception to the injunction and basis for the Society's review

The terms of the exception agreed by Imutran and authorised by the Court allow Dr Maggy Jennings to review all the material relating to the Diaries of Despair report downloaded by the RSPCA from the Uncaged website, and to prepare a report on it. In so doing, Dr Jennings was permitted to consult Imutran, Huntingdon Life Sciences and Uncaged Campaigns. Also able to see all the material were Drs Mark Prescott, Vicky Robinson and Penny Hawkins of the RAD, Dr Arthur Lindley, Director of Science and Dr Tony Suckling, Deputy Director General[10].

The positive response from Imutran to the Society's application for an exception was at least in part due to the expertise and authority available to the RSPCA through its professional staff. The RAD comprises scientists qualified to PhD level in scientific disciplines relevant to xenotransplantation as a whole and to the subject matter of the Uncaged report. The authors expertise includes primatology, virology, physiology, pain recognition and assessment, transgenic technology, ethics, and the operation of the Animals (Scientific Procedures) Act 1986 (ASPA)[11]. RAD staff regularly visit establishments where research is carried out and initiate and participate in working groups on laboratory animal husbandry and care, pain recognition, cost/benefit assessment, licensee training and many of the other issues raised by the Uncaged

report and discussed here. Dr Maggy Jennings is a member of the APC and UKXIRA, which are both concerned with the regulation of xenotransplantation in the UK, and of the Council of Europe Working Group on Xenotransplantation. Dr Tony Suckling was a member of the APC during the period covered by Imutran's early project licences, and was a member of the Kennedy Committee on xenotransplantation[12].

A second important consideration with respect to the exception was the intended focus of the proposed RSPCA report. The Uncaged report targeted its criticism specifically at HLS, Imutran and the HO, but Society staff considered that the majority of the issues were widely applicable to the regulation of research in general and should be viewed in that context. It was therefore stated in Dr Jennings' witness statement that the Society's report would focus specifically on *"the implications of the material for the implementation of ASPA"* and that it would include discussion of the following:

> *"(i) How the cost/benefit assessment under ASPA is applied by the Home Office, scientists, the company, and the Animal Procedures Committee.*
>
> *(ii) The factors taken into account when carrying out the cost/benefit assessment.*
>
> *(iii) The level of suffering endured by these primates, whether this was adequately predicted and what weight it was given.*
>
> *(iv) The arrangements for ongoing monitoring and review of procedures and their results. How this is communicated to the Home Office and in this instance APC and UKXIRA. Whether there were any discrepancies in the process with the research described in the report.*
>
> *(v) On what basis the continuation of these experiments was considered to be justified despite such apparently short survival times and poor quality of life for the animals involved.*
>
> *(vi) How a major pharmaceutical company such as Novartis 'interprets' the requirement to minimise animal suffering integral to ASPA; what attempts were made to ameliorate the suffering of these primates?*
>
> *(vii) Whether any of the people involved in this research were concerned about levels of animal suffering and whether there was a mechanism to deal with such concerns.*
>
> *(viii) How the requirements for competency are addressed by Imutran, the Home Office and the establishments where research was carried out.*
>
> *(ix) The nature of the information requested by and supplied to the APC and UKXIRA individually.*
>
> *(x) Primate supply and transport issues.*

(xi) The carrying out of the procedures on the animals and the husbandry and care of the animals.

(xii) The roles of and inter-relationship between the APC, UKXIRA, the Home Office and the Department of Health in respect of xenotransplantation generally and in particular the objectives of the research as regards the survival times and quality of life of the animals in pre-clinical studies".

Furthermore, the RSPCA is recognised as a responsible and authoritative organisation to whom members of the public look to provide a balanced account of matters of concern relating to animals and their welfare. This includes the issue of xenotransplantation.

3. Description of the material available to the RAD

3.1 Imutran documents supplied by Uncaged

The leaked material includes: correspondence; minutes of Imutran meetings where research is discussed; internal reports, and feasibility studies concerning many aspects of the conduct of, and plans for, xenotransplantation research; two proposals for MD theses on xenotransplantation; and letters and reports to the HO regarding the existing project licence and the proposal to renew this licence. Some of these documents are in draft form, some are only partly legible, and some are incomplete in that they comprise a letter, memo or e-mail without the subsequent response.

There are, in addition, the draft reports of 39 xenotransplantation studies carried out by Imutran at HLS. These are the most significant documents since they contain information about the research itself. The reports describe the aims of each study and how it will be carried out, and set out the results in a series of tables containing details of various biochemical and physiological measurements taken from the animals used. There is also a table showing the notes made during the daily observation of the clinical signs for each animal recorded 'a.m.' and 'p.m.'.

3.2 The Uncaged report – Diaries of Despair

Diaries of Despair is a one hundred and fifty seven page report which sets out to analyse and interpret the leaked material. It is divided into five parts:

Part 1 'sets the scene', providing a background to xenotransplantation, ethics and the regulation of animal experiments.

Part 2 covers the research on baboons including their acquisition, importation and confinement in captivity; biohazhards; and the research itself.

Part 3 covers research on cynomolgous macaques and their importation.

Part 4 relates specifically to HLS and covers issues such as: the conduct of research; the relationship between Imutran and HLS; Good Laboratory Practice (GLP); errors and procedural failures.

Part 5 presents the report's conclusions and recommendations.

3.3 Material provided by Imutran

Imutran prepared a twenty-four-page analysis of the Uncaged report, which responded to many of the points and questions raised. This analysis was made available to the Court, the HO, APC and UKXIRA as well as to Uncaged and the RSPCA.

Video footage[13] (2 minutes) of one baboon who had undergone heterotopic cardiac xenotransplantation (pig to primate heart transplant) and who survived for 39 days was provided to the RAD on request. The surgeon's notes on this individual were also supplied. We asked Imutran to provide the surgeon's notes for the other five animals on the particular study for comparison but they were not willing to do so.

3.4 Other information

In addition to the leaked materials, the Uncaged report uses information currently available in the public domain, such as the Home Office Annual Statistics of Scientific Procedures on Living Animals in Great Britain and Hansard House of Commons debates. RAD has access to the same information.

Dr Maggy Jennings' membership of both the APC and UKXIRA means that she has also been party to discussion of many of the points raised in the Uncaged report both prior and subsequent to its release and has had access to additional documents. Information provided to both APC and UKXIRA is confidential in that it cannot be used in this RSPCA report unless it has subsequently entered the public domain through the reports or web sites of either authority. It will however be included as additional material in a separate report by Dr Jennings to the HO and the APC.

RAD staff (Drs Jennings and Hawkins) had made an informal visit to the facilities at HLS in 1999, and Dr Jennings had seen and discussed the primate housing in current use for both stock and experimental animals. Dr Jennings had also seen the facilities for xenotransplantation research. Dr Jennings visited HLS again in January 2002 with Dr Prescott to discuss concerns surrounding the xenotransplantation work. All RAD staff also participate in meetings and workshops where many of the issues raised in the report, in particular relating to the operation of the ASPA, are discussed.

During the period from 1997 to 2000, Dr Jennings together with Dr Wrathall, deputy head of the RSPCA's Farm Animals Department, liaised with the personnel at Imutran with responsibility for the husbandry and care of the pigs used in the xenotransplantation research programme. This was with respect to work within RAD and their membership of the HO working group developing standards of husbandry and care for these animals[14]. We received the information we asked for from Imutran with regard to the pigs and had constructive discussions regarding the incorporation of environmental enrichment into the husbandry systems used. We have not had similar discussions regarding their research on primates.

The report of the Chief Inspector was published in July 2001 and is publicly available on the HO website.

Xenotransplantation and some of the work of Novartis in this respect was discussed in three, one hour, documentaries shown by Channel 4 in June 2001. These documentaries contained considerable footage of pig to primate transplants, similar to those carried out in the UK and reported on by Uncaged. Some of the video footage of the surviving baboon mentioned in 3.3 above was shown as part of the documentaries.

4. Brief description of the research

The research carried out by Imutran and covered in the background material available to the RSPCA involved the transplantation of either pig hearts, kidneys, pancreatic islets and/or bone into baboons or cynomolgous macaques. In an early experiment cynomolgous' hearts were transplanted into baboons. The transplants were either heterotopic (when the primate's own organ was left *in situ*) or orthotopic (when a pig organ was used as a complete replacement for the primate's own organ). A hetrotopic transplant can be used to assess whether a transplant is rejected, whereas an orthotopic transplant experiment will also demonstrate whether the transplanted organ is life supporting. Both types of transplant may be used to study the many aspects of rejection. Most transplant experiments involved the subsequent administration of different immunosuppressant treatments to try to prevent rejection and prolong survival of the organ/tissue and hence the transplanted animal.

All the research was licensed by the HO under the ASPA and, as is routine practice for these sort of projects, had been reviewed prospectively by the APC. As such it would have been first discussed by the APC Primate Sub-Committee before being passed to the full Committee. Some of the research had also been referred to UKXIRA for advice.

The research was known to be of sufficient severity to warrant an initial substantial and later moderate classification and its justification was assessed on that basis.

A definition of xenotransplantation and of some of the main terms and conditions of the ASPA are given in Appendix A.

5. Method of review and issues of confidentiality

The injunction permitted RAD staff to *"review the material relating to the Diaries of Despair report downloaded by the RSPCA from the Uncaged website and to prepare a report on it"* and this is what we have done.

We (the authors), took the view that we should first review the background material on which the Uncaged report was based and form our own conclusions, rather than start with the Uncaged report which had collated and interpreted the background information. We then compared our conclusions with those put forward in Diaries of Despair, to focus on the issues of concern we felt should be pursued further.

The background material only presents a 'snapshot' of Imutran's xenotransplantation research. Information on the specifics of the research and on matters such as how and

why it was done, how the regulatory controls were applied, and the level of monitoring is very incomplete. Much of the material is labelled as 'draft' and the correspondence in general is fragmented, often with only parts of the exchange present. This makes it impossible for a body such as the RSPCA to analyse fully what happened to the animals involved with this research and for what reason, or the levels of compliance with relevant legislation and codes of practice. A full investigation of this sort can currently only be carried out by the HO, as the authority responsible for the administration of the ASPA.

It is particularly important to note here that compliance with legislation was not the only, or even the main consideration in our review. There is enough information to identify a whole series of issues and concerns with respect to the way the current regulatory system (against which compliance is assessed) operates, particularly with respect to xenotransplantation and the use of primates in experiments, and this has formed the basis of our report. However, we would draw attention to the constraints that the confidentiality in the administration of ASPA imposes on these issues that are of clear public concern.

We carefully examined the Imutran response to the points and questions raised by Uncaged and the report from the Chief Inspector when this became available. In some cases the Imutran response clarified what was obviously a misunderstanding, either of terminology, or as a result of Uncaged having access only to the leaked documents. In many cases there is clearly a difference of opinion between Uncaged and Imutran regarding the points made by the former and the response of the latter. The RAD has not set out to adjudicate between Uncaged and Imutran on these matters unless we believe there is sufficient information on which to form a view.

With respect to the Chief Inspector's report, this dealt only with the specific details of Imutran's compliance with the licence authorities issued under the ASPA, whereas our concerns are much wider. The Inspectorate review involved *"in excess of 250 man hours of work and included seven visits to Imutran to view original study documents and interview management and staff, and four visits to other sites."*. It is important to note that in preparing his report, the Chief Inspector 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 HO. The majority of this information remains confidential and cannot be divulged to the RSPCA.

Drs Jennings and Prescott visited HLS in January 2002 to discuss our concerns. We were unable to provide HLS with a full list of our points and questions, or a copy of our draft report, since the injunction in force would not permit this. This inevitably inhibited our discussion, although HLS staff were very co-operative and we have included information from HLS where this would not be a breach of confidentiality.

Because so much of the information relating to this issue remains confidential under ASPA, we have set out many of our concerns in the ensuing chapters as a series of questionssome of which (particularly with regard to decisions on end-points, monitoring of animals and staff training and expertise) we have already discussed with the Chief Inspector, HLS staff and within the APC. Nevertheless, we believe the RSPCA should not be the only public body party to the information we have received. Moreover, all of the points and questions raised need further in-depth discussion in the public domain.

Throughout our analysis we have tried to make an objective assessment of the factual information supplied, whilst recognising that this information is incomplete. We have tried not to respond to assumptions or conjectures since this would lessen the value of our report. Our approach is obviously from an animal welfare perspective.

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Part B

RAD analysis of the documents downloaded from the Uncaged website in relation to xenotransplantation in general and the ASPA in particular

1. Introduction

Part B examines each of the broad areas of concern raised in the Uncaged report. These are:

- Xenotransplantation as an issue of public concern (see Section 2 - note that public interest issues in relation to the ASPA and its implementation are discussed in Section 4);
- The welfare implications associated with the acquisiton, importation and confinement of primates, including wild-caught baboons (Section 3);
- The implementation of the ASPA and the adequacy and effectiveness of this legislation (Section 4);
- Matters relating to HLS (Section 5);
- The biohazhards associated with primate use (Section 6).

These concerns, and indeed much of the information on which they are based are not new. They have been discussed and reported on elsewhere in the public domain. The unique interest of the Imutran documents upon which the Uncaged report is based is that they contain descriptions of the experimental protocols and the clinical signs observed in the animals. This provides a more comprehensive picture of what this sort of research actually means to the animals involved than was available hitherto. We believe it imperative that information regarding the full impact of xenotransplantation research on the animals concerned should be in the public domain to enable a more realistic assessment of the harm/benefit evaluation and hence of the justification and ethical acceptability of the research.

Note that although this work was carried out at HLS and therefore involved HLS facilities and staff, Imutran initiated the research and were responsible (as holders of the project licence) both for setting out the cost-benefit assessment of the research under ASPA, and for its conduct.

2 Xenotransplantation as an issue of public concern

2.1 Controversy and public consultations

The Uncaged report describes xenotransplantation research as being controversial for a number of reasons relating to: the use of primates in research; the use and welfare of pigs as source animals; the scientific assessment of xenograft compatibility and function; the risk of transference of disease agents from animal to humans; and the

use of the technology with respect to the overall approach to human health problems. Without doubt xenotransplantation is a controversial issue - the points that the Uncaged report raises in this regard are not new. They have been, and continue to be, discussed in detail and from a variety of perspectives, both in the UK and internationally. Consideration of the risks associated with xenotransplantation and of issues such as patient consent and monitoring have formed a major part of the work programme of the UKXIRA since the Authority was established in 1998 and of regulatory bodies in Europe, Canada and the USA. There are a number of published articles and reports, which set out and discuss all these issues [e.g. 12,15-18].

Uncaged also describes xenotransplantation as a matter of wide public interest and concern. This is clearly true for a whole variety of reasons. Indeed, in the early 1990s, development of the technology prompted the setting up of two independent reviews, both of which undertook wide consultation. The first was carried out by the Nuffield Council on Bioethics[15] and the second by the Advisory Group on the Ethics of Xenotransplantation (the Kennedy Committee)[12]. Both committees published authoritative reports. Although both concluded that xenotransplantation was "*ethically acceptable*", this was not without certain provisos which included the humane treatment of animals. In the case of research on primates, it also included the need to minimise animal use and associated suffering. Furthermore, the need for regulation of the technology was recognised, and UKXIRA was set up by the Government as a direct response to the recommendations of the Kennedy Committee.

The fact that these committees were set up, that they undertook a public consultation exercise, and that a National Authority was established to regulate xenotransplantation (UKXIRA) as a result, demonstrates that this issue has been recognised for some time as being of major public interest and concern. The concern expressed by the public and the interested 'stakeholder' groups encompasses animal welfare and animal rights as well as medical, ethical, social and economic perspectives. The RAD would, therefore, endorse the statement made on page 13 of the Uncaged report that:

> *"There is a clear public interest in the ethical issue of how our society treats non-human animals. Moral responsibility and public debates seeking to ascertain the nature of such responsibilities are inescapable aspects of the human condition. They define who we are and how we value and feel about our society and ourselves. A significant proportion of the public do take a deep interest in the treatment of animals."*

The Uncaged report and the material on which it is based is therefore relevant to the issue as a whole and to how xenotransplantation is presented in the public domain.

2.2 Decisions on ethical acceptability of xenotransplantation as a technology

At the time that the Nuffield and Kennedy committees were reporting, it was thought that clinical xenotransplantation was imminent and that it would deliver great benefit to patients awaiting organ transplantation. In fact, Imutran had announced in 1995 that a move to clinical trials was likely within the following year and this statement is quoted in the preface to the Nuffield Council report *Animal to Human Transplants: the ethics of xenotransplantation*[15]. We believe that as a result, the discussion relating to the implications of xenotransplantation for animals, and its ethical implications in this respect, focused on the animals who would be used as a source of organs or

tissues, rather than issues associated with the use of animals in the research to develop and evaluate the technology.

It was noted in both the Nuffield Council and Kennedy Committee reports that research on primates would be required to continue the development of the technology. However, the likely extent of this in terms of the number and level of suffering of the animals involved was apparently not recognised and discussed, or at least not reported, in detail. Either way, neither report gives any real 'feel' for the nature and levels of suffering primates (and other animals) endure in xenotransplantation research. The recommendations from the Kennedy Committee, which were accepted by the Government[19], did however stress the need to co-ordinate research so as to minimise the use and suffering of primates. Recommendation paragraph 33 and 4.98 of the Kennedy Committee report stated:

> *"We take the view that further research involving primates should be kept to the minimum necessary, and that, wherever appropriate, other means of generating reliable information be used. We also recommend that the welfare of the animals used should be closely monitored and supervised."*

In deciding on the ethical acceptability of xenotransplantation (or any medical technology for that matter) it was, and is, necessary to weigh the harms and/or risks that might incur (including those to animals) against the perceived benefits expected to be obtained. In order to do this there must be a full and clear understanding of what the harms, risks and benefits are likely to be. The need to gain this understanding provides the impetus for a vast amount of research in a wide range of fields (including studies on efficacy, physiology, immunology, and infectious risks). This research will encompass a wide range of methods, some of which involve the use of animals and will be carried out on an international basis. Consideration of the full impact for animals therefore has to take into account the nature of research carried out worldwide.

In the case of xenotransplantation, the full 'costs' to animals both as sources of xenografts, and in particular in the associated research, are unquestionably extremely high - the leaked study reports and the Uncaged report, graphically describe the suffering of the primates used as, in fact, do published research papers on this issue, albeit expressed in more technical scientific language. However, it is our view that the nature of these harms – the summation of all the adverse effects – have hitherto not been fully appreciated in terms of understanding and acknowledging what the animals really experience. We believe that as a consequence, the harms have not been adequately assessed in the overall harm/benefit evaluation of xenotransplantation as a technology (note, this is in addition to, and separate from, the specific cost/benefit assessment for individual projects required under the ASPA).

The Kennedy Committee report stated that the acceptability of xenotransplantation depended on the full evaluation of its costs and benefits, and it emphasised that such assessments are not 'one off'. We believe that a stringent and critical re-evaluation of this issue is long overdue. We believe it imperative (as do Uncaged) that information regarding the full impact of xenotransplantation research on the animals concerned should be in the public domain, otherwise people cannot make a fully informed judgement on whether they believe the development of xenotransplantation to be morally acceptable.

2.3 How research progress is presented to the public

Another issue raised by the Uncaged report is that Imutran as a company, and the scientists involved in the research, have 'talked up' the research such that progress towards human trials (the benefit) has seemed much more likely than is in fact the case, and that this 'deception' has been going on for many years. One criticism, made by Uncaged and justifiable in our view, is that this creates false hope for those patients and their families awaiting a transplant. A great deal of responsibility for this exaggeration of the rate of progress, however, must lie also with the press and media, who actively seek to publish high-profile articles on the imminence of successful xenotransplantation.

Misrepresentation in the media is not unique either to the work of Imutran, or to xenotransplantation (or, for that matter, to science and industry). It is a problem with the way the press and other media handles the reporting of science in general, including and especially medicine and biotechnology. Indeed, the issue of the reporting of medical and scientific issues to the public was addressed in an international conference of national medical ethics committees in Strasbourg in 2000[20]. Such matters are discussed and encompassed within disciplines such as medical and social ethics and have also been considered by UKXIRA.

The Uncaged report also criticises Imutran for not acknowledging the extent of the suffering of animals in the research. This is also true of our experience of the statements made by the company outside of the scientific community and within the public domain. The RAD has itself strongly criticised an Imutran leaflet for not acknowledging the animal suffering associated with the development of xenotransplantation. This is a specific example of a general point. In our view spokespersons for science and industry are far more willing to talk of the potential benefits of their research than they are to acknowledge the potential, or in this case very real, harms to the animals involved.

In order to make informed decisions on the ethical acceptability of xenotransplantation, both for themselves 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 the implications for laboratory animals. The Uncaged report also draws this conclusion. The difficult question, and one that is also asked within bodies such as UKXIRA and the EU working group on xenotransplantation, is how the public can be made aware of the full implications of any area of medical research when there are always so many different and competing interest groups involved.

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 clearly necessary. This must however apply to all interested parties including animal protection groups.

3. Welfare implications of the acquisition, importation and confinement of baboons and macaques

Between 1996 and 1998, Imutran used a total of forty-nine wild-caught baboons in xenotransplantation research. Between 1996 and 2000, four hundred and twenty four captive-bred cynomolgous macaques were also used. The material leaked from Imutran contains details of, and correspondence with, the suppliers of these animals and other bodies such as the HO and the Ministry of Agriculture, Fisheries and Food (MAFF) (now the Department for Environment, Food and Rural Affairs (DEFRA)), who have complementary responsibilities in the area of primate importation to the UK for use in research and testing. Correspondence relating to shipment details is also included in the leaked material and this has been interpreted by Uncaged in the light of additional information, for example answers to parliamentary questions. We must stress again that in our analysis of this information we have used only the factual material and our experience of laboratory primate issues.

The two issues of concern raised by this particular material are: (i) the source of the imported primates; and (ii) the conditions of transport during their importation. Both of these issues are matters of concern to the public at large, and in particular to the RSPCA, because of the implications they have for animal welfare[21,22]. There is no doubt that both sourcing (capture from the wild or breeding in captivity) and transport can and do cause animals suffering and distress. Note that these are additional harms over and above those relating to experimental use that must form part of the weighing of harms and benefits. This is reflected in the fact that both are regulated by the ASPA and other regulations (e.g., Animal Health Act 1981; Welfare of Animals During Transport Order 1997; International Air Transport Association (IATA) Live Animals Regulations; Regulations implementing the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)). Moreover, in 1996 the UK Government banned the importation of wild-caught primates for use under the ASPA (unless the project licence applicant can establish exceptional and specific justification for their use). The perceived benefits of xenotransplantation (see Section 6 of this report) and the perceived scientific need to use animals as closely related to humans as possible, and of suitable size, would have presumably provided the basis for the requisite "exceptional and specific" justification for the use of wild-caught baboons.

Given the obvious level of concern over these issues, one would have hoped and expected that the animals used by Imutran would have received particular sympathetic and empathetic treatment within their research programme.

3.1 Source of animals

The baboons used by Imutran were wild-caught animals supplied by a wildlife dealer near Nairobi, Kenya. The use of wild-caught animals raises serious animal welfare issues relating to high incidence of death, injury and suffering as a result of methods of capture; handling and restraint; isolation; social disruption; crowding; confinement; prolonged human proximity; lengthy waits in transit; loading and transport; and unfamiliar and inappropriate diets, housing and environmental conditions[23]. The high incidence of mortality, injury and suffering for wild-caught primates has been recognised widely for a number of years such that, as stated above, a ban on their use in research in the UK was implemented by the Government in 1996[24].

The macaques used by Imutran were captive bred from Mauritius, the Philippines and Indonesia. It should be noted that the use of captive-bred animals in itself does not avoid a demand for wild-caught animals, since individuals are taken from the wild to set up breeding colonies and to supplement the breeding stock of established colonies.

The Uncaged report highlights two important points relating to the source of animals both of which the RAD is aware of and has already addressed in a separate detailed report on the welfare implications of primate acquisition and transport[22]. These points are discussed briefly in 3.1.1 and 3.1.2 below. A third point regarding the establishment of a South African captive breeding centre for baboons (of which we are also aware) is addressed in 3.1.3.

3.1.1 Home Office authorisation of overseas sources

Since 1996, acquisition of primates from overseas sources has had to be authorised in advance by the Home Office[24]. In practice, this means that overseas breeding and supplying centres have to comply with certain minimum standards of housing, husbandry, care and transport. This was one of the recommendations made in the 1994 RSPCA report on the international trade in primates for research and testing '*The Supply of Non-Human Primates for Use in Research and Testing: Welfare implications and opportunities for change*'[21]. The source for the baboons used by Imutran was visited by the Home Office Inspectorate (HOI) in 1995 and was considered unsatisfactory[25]. The supplying centre was advised that improvements in the standards of housing, husbandry and care would have to be made in order to be permitted to supply animals to the UK.

In February 1997, the centre was approved by the HO on the basis of documentary evidence of improved facilities[25]. However, the documentation had been supplied by those, including Imutran, who wished to use animals from the centre. It seems extraordinary to the RAD that the HO relied on information, supplied by user establishments, in its decision to approve the breeding centre, rather than HO inspectors visiting it in person. It also seems extraordinary given the additional 'protection' granted to primates by the ASPA, that <u>all</u> facilities supplying them are not regularly inspected. We believe this to be a serious failing of the regulatory system, whether it reflects inadequacy in the numbers of inspectors available to make such visits, or the level of priority given to this issue. The HO presumably would not license a UK breeder or supplier on the word of a user establishment and the same standards should apply on an international basis.

We understand the APC Primate Sub-Committee has sourcing of primates in its work programme and we seek assurance that the issue of inspection of overseas centres is addressed as a matter of urgency. We also believe that now the number of HO Inspectors is being increased to 33, regular visits to overseas primate suppliers should be an essential part of their work for as long as primate imports continue.

3.1.2 An ethical dilemma regarding 'third countries'

The second point relating to the source of primates highlighted by Uncaged is that only those primates destined for use in the UK were held in the 'improved' facilities mentioned above. The majority of baboons were held in caging of lower standards. These were animals destined for use in countries such as the USA, whose scientists

and regulators are prepared to use and/or accept data from animals, despite the additional insult to the primates concerned, of confinement in inadequate housing prior to transport.

We are adamant that primates supplied to the UK from overseas should only be sourced from facilities whose standards of housing, husbandry and care are at least equal to the UK Code of Practice for Laboratory Animal Breeding and Supplying Establishments[26] and who also comply with the International Primatological Society (IPS) International Guidelines for the Acquisition, Care and Breeding of Nonhuman Primates[27].

Unfortunately, overseas breeding and supplying establishments supply animals to a number of countries. The UK has no jurisdiction over animals bred or kept in countries outside of the UK and who are destined for supply to third countries. UK users as prospective 'customers' and the HO as UK regulators, however, do have the opportunity to exert pressure on breeders and suppliers to improve their standards. We understand that the UK has had some beneficial influence on standards overseas but we do not believe enough is done in this respect.

There is, then, a serious question: whilst primate use continues, should UK scientists and/or institutions continue to be allowed to use suppliers that do not meet UK standards for all their animals, in order to enable responsible users and the HO to exert what influence they can in favour of improved standards, or should such overseas suppliers be disallowed altogether, regardless of whether there is an alternative source? And would the UK Government have the power to do this? The one point that is clear is that in order to ensure that the best deal for animals is secured, the consequences of any action regarding the sourcing of primates from overseas must be fully evaluated before any decisions are made.

These are further questions we urge the APC to consider in depth. Primate users, ethical review processes, the HO and the IPS should all use every opportunity to exert additional pressure on breeding and supplying establishments to raise their standards. Now that Novartis is operating in the USA, it should live up to its claims of concern for animal welfare by using its influence to raise the standards for primates destined for laboratories in that country which is one of the largest users of primates in the World.

3.1.3 A South African breeding centre

The Uncaged report also describes the plans of the South African Government's Medical Research Council to set up a captive-breeding centre for baboons at its animal centre in Delft, South Africa. The intention is to ensure a ready supply of these primates for xenotransplantation research in other countries and/or in South Africa itself. The plans are common knowledge amongst the animal protection community and have already been opposed by the South Africans for the Abolition of Vivisection (SAAV). Uncaged criticises the plans and suggests that captive breeding centres "*entrench the prejudice that baboons are merely instruments of technology*...". We agree. We believe that there is a distinct tendency, if animals are available, to find a use for them.

The Uncaged report's main questions on this issue, however, focus on whether the UK scientific community, the British Medical Research Council and the HO, support the proposed centre and, if so, whether this is an appropriate and ethical stance to adopt. In fact, the UK scientific community as a whole is unlikely to have a view on the plans, since such a centre would only be relevant to a relatively small number of scientists working within a few specific disciplines. RAD can ask the HO for a view on its position but, in a sense, this view is unimportant, since the HO has no jurisdiction over animal research in South Africa, and no jurisdiction over UK researchers who wish to work there.

By drawing attention to the plans, the Uncaged report illustrates a specific example of the more general issue of researchers moving their research abroad or collaborating with scientists operating under less detailed legislation overseas. This issue is an important one, particularly since research programmes are increasingly conducted on an international basis. It has been discussed by a number of groups in the UK including the APC, UKXIRA and the Boyd Group, although no conclusions on how to address the issue have yet been reached.

3.2 Transporting and importing primates

With regards to the conditions of transport for imported primates, the Uncaged report tells us little that RAD did not already know and that we have not already reported on in the public domain[21,22], other than details of individual import approvals and journey times, and comments by named individuals. In our view several of these comments (taken from internal memos) expressed an inappropriate attitude by Imutran staff to the animals they wished to import. The extra sympathy and empathy that ought to have been warranted by the use of wild-caught primates was conspicuously absent. Other than this, the issues raised relate to primate transport and use in general and not specifically to Imutran and/or HLS. They are nevertheless extremely important - the entire process of capture, temporary confinement and transport is likely to be highly stressful for both baboons and macaques and is therefore a matter of serious concern that must be addressed as a matter of urgency.

Regulation of the trade in primates is complex. In the UK, prior to the June 2001 General Election, it was regulated by several Government departments, including the HO, the Department of the Environment, Transport and the Regions (DETR), and MAFF. It is now regulated by the HO and DEFRA. The RAD is in correspondence with both of the departments over its concerns regarding primate trade and has had useful and informative discussions with the Home Office Inspectorate. Our new report on primate trade[22] has been submitted to both Government departments for a response to the concerns and recommendations contained therein. These can be broadly grouped into those relating to welfare conditions in source countries, welfare conditions during all stages of transportation, the efficiency of the present trade monitoring system, and the application of cost-benefit judgements under ASPA.

Two additional and specific transport issues raised in the Uncaged report are: (i) an apparent disparity of numbers imported and recorded; and (ii) deaths in transit. These are discussed below.

3.2.1 Disparity in numbers imported and used

In recent years, there have been a series of parliamentary questions about the import and use in research of wild-caught primates. The Uncaged report suggests that there are alarming discrepancies between figures on primate use obtained from the Imutran data and figures given in a Hansard report of a written answer to a parliamentary question[28]. The Uncaged report also raises questions about the eventual fate of some primates imported into the UK, and in particular that of twenty-eight baboons imported to HLS in 1999 but not subsequently used there.

We checked carefully the figures quoted in the Uncaged report against CITES import permit data from the DETR[29]. This showed that the figures reported in the Uncaged report were likely to be correct, but that those in the Hansard written answer were not. The discrepancy may have resulted from an inadvertent error. Answers to some of the other questions described by Uncaged as "*suspicious*", such as the eventual fate of the twenty-eight baboons, were likewise investigated by RAD. We are satisfied that these animals were, in fact, exported for use elsewhere. We consider this transitory movement of animals to be totally unacceptable in view of the likely impact on animal welfare, but it was nevertheless authorised and documented correctly.

The issue of primate transport provides an example of where the real question is not about Imutran and HLS's compliance with the existing legislation, but is about whether the legislation they have to comply with is adequate to afford animals the level of protection that they deserve.

3.2.2 Deaths in transit

There is much discussion in the Uncaged report about the death of macaques in transit to the UK, particularly regarding three animals who died in 1998. According to the HO Minister, eight cynomolgus macaques have died during transit to the UK since 1995[30]. The Uncaged report is critical of the HO's response to these deaths, describing it as "*feeble*". Much of Uncaged's argument is based on supposition founded upon answers to parliamentary questions, together with correspondence to Uncaged from Imutran.

We agree that the death of primates in transit is totally unacceptable, and furthermore, that there must be a stronger system of regulation in place to prevent this occurring in the future. However, from our reading of the background material and other information available to us, it appears that HLS and the HO in fact acted quickly and appropriately in this instance. There are, of course, important questions arising concerning the effectiveness of existing transport regulations and the sanctions that are applied when such tragedies occur. These are issues that we are currently exploring through our Counting the Cost report[22] and through liaison with the HO, DETR, MAFF, and now DEFRA, as part of our work on primate trade.

The difficulty in obtaining a satisfactory response to questions about the death of the macaques provides an illustration of instances in which there is insufficient information available within the public domain, or where information is not easily accessible, in order for interested parties to make a judgement as to whether or not controls are adequate and/or appropriately applied. Parliamentary questions are of course one possible source of information, but answers to these are often frustrating in that they fail to clarify the situation since, by their very nature, they are too brief to provide a full explanation.

3.3 Conclusions

The RSPCA believes the whole issue of primate acquisition and transport needs to be urgently re-evaluated by those with responsibilities for regulating it. The points made in the Uncaged report are a specific illustration of general problems which have been raised previously by the RSPCA and others, most of which are already in the public domain.

Under the ASPA, the use of primates requires special justification and the suffering of those used must be minimised. If either issue is to be properly addressed, then it is essential that all involved with primate use must first be aware of all the stresses imposed on animals by virtue of their use in experiments. For these reasons, it is also important for project licence holders, ethical review processes, regulatory and funding bodies to take greater responsibility for the primates used by or for them, and to ensure that they are fully aware of, and give due consideration to, all of the costs to the primates involved, including those due to acquisition and transport. It is then incumbent upon them to ensure the highest standards of welfare for these primates at all stages of their acquisition and transport.

The RSPCA's recently published report on primate acquisition and transport reviews progress since the Society's 1994 report on this issue was published, and makes substantive recommendations for further action by those involved in carrying out and/or regulating experimental procedures on primates. The recommendations cover all of the points above and so are not repeated here. They are aimed at improving upon the current situation and preventing problems such as those detailed above. We would ask the DEFRA, the HO, and the APC in particular to consider these issues as a matter of urgent priority.

4. Implementation of ASPA and the adequacy of the legislation

There are two general themes that run throughout the Uncaged report:

i) the extent of, and justification for, the animal suffering described; and
ii) the inadequacy of the legislation in preventing such suffering.

Both points have broad implications for the issue of animal experiments in general, as well as for the specific xenotransplantation research carried out by Imutran. The Uncaged report raises many concerns relating to the way the studies were designed and carried out, the management of the project licences, and the monitoring and reporting of animal studies. These are mainly contained in the sections dealing with the research on macaques and baboons (Uncaged Report Sections 4 and 5) and represent fundamental concerns about the way the ASPA is implemented. As such they are not specific to Imutran or HLS and, in fact, reflect long-standing concerns for the RSPCA regarding research and testing in general and how the provisions of the Act are interpreted and implemented in practice (see also Part A, Section 5 of our report). They also encompass the subjective nature of the cost-benefit assessment, and the question of subjecting animals to severe pain. We deal with these and other matters in Sections 4 to 9 of our report, which address xenotransplantation research in

the context of how it is regulated under ASPA and the Uncaged report's criticism of this.

However, for a proper and complete analysis of the way this particular programme of research was licensed, managed, monitored and controlled it is necessary to have access to all the relevant documentation and to have been party to the discussions which this project would have necessitated and particularly to the views of the HO Inspectorate (and the APC and UKXIRA). No analysis can be complete without this input, most of which will be confidential to the licensing authority, and we have found that our assessment has raised more questions than it has answered. We have identified the most important questions throughout the text and believe it is absolutely essential that these be addressed by the relevant regulatory authority/s. Furthermore, those who actually carry out research on animals and who are responsible for generating and designing the studies also have a legal and moral responsibility to seriously address these same questions. This applies to all research wherever it is carried out, but with respect to xenotransplantation, we believe that Imutran/Novartis 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. In so doing the company should obtain the input of those experienced in primate health, welfare and behaviour to help properly assess the level of primate suffering.

4.1 Key questions

There are three key questions posed in the Uncaged report which have a bearing on the regulatory framework of the ASPA. These are summarised below since they represent points that recur throughout both the Uncaged report and our own:

(i) Can the deliberate infliction of suffering and death on other animals, not least non-human primates, ever be justified?

(ii) To what extent has the ordeal of the primates used in this research project transgressed the 'absolute ban' on severe pain and distress in UK and European legislation?

(iii) How fairly and honestly has the Home Office implemented the cost-benefit analysis and the 1986 Act in general, and specifically, with regard to xenotransplantation?

The first point is not in fact exclusive to the use of animals in experimental procedures. It is an important moral question on which there is a very wide spectrum of views ranging from an absolute "no" to an absolute "yes". There is unlikely ever to be total consensus about what it is acceptable to do to animals, but we agree with Uncaged that it is important for a humane society to keep asking this question.

Current legislation, which is supposed to reflect the majority societal view at the prevailing time, permits research on animals within the regulatory framework of the ASPA. Animals can be used in experiments likely to cause them pain, suffering, distress and lasting harm but not without certain constraints. The second and third points listed above relate to whether these constraints operated effectively in the xenotransplantation studies. Both points have general implications with respect to

implementation of the ASPA, whether these be in terms of the xenotransplantation research reported here, or more widely to all research. For the RAD, these points are the two key issues in our assessment of the leaked material, and both points will be addressed in more detail later. It is important to begin by defining the principles with which they are concerned, because these are of such importance to the rest of this report.

The ban on severe pain

Paragraph 5.42 of the Guidance on the Operation of the Animals (Scientific Procedures) Act 1986[11] states:

> "*The Secretary of State will not licence any procedure likely to cause severe pain or distress that cannot be alleviated* ".

The section of the ASPA to which this statement refers (Section 10(2A)) explains that the personal licence shall include such conditions as the Secretary of State considers appropriate to ensure that authorised scientific procedures are carried out in accordance with Article 8 of the European Directive 86/609[31] which states that:

> *"If anaesthesia is not possible, analgesics or other appropriate methods should be used in order to ensure as far as possible that pain, suffering, distress or harm are limited and that in any event the animal is not subject to severe pain, distress or suffering. Provided such action is compatible with the object of the experiment, an anaesthetised animal, which suffers considerable pain once anaesthesia has worn off, shall be treated in good time with pain-relieving means or, if this is not possible, shall be immediately killed by a humane method".* •

The personal licence also makes it beholden on the personal licence holder to prevent or reduce to the minimum consistent with the purposes of the authorised procedures any pain, distress or discomfort to the animals to which the procedures are applied; and also contains an inviolable termination condition which specifies circumstances in which an animal being subjected to a regulated scientific procedure must in every case be immediately killed by a humane method appropriate to the animal.

This appears to mean that if an animal is suffering severe pain, which is not temporary and cannot be alleviated, he or she must be humanely killed at once, regardless of how important the animal is for the experiment. It is not clear, however, how this relates to the fact that procedures classified as substantial, described in the Guidance on the Operation of the ASPA (Paragraph 5.4.2) as those "*that may result in a major departure from the animal's usual state of health or well-being"*, including: "*acute toxicity procedures where significant morbidity or death is an end-point…major surgery",* and "*some models of disease where welfare may be seriously compromised*", are allowed.

- Note, that RAD staff believe this Article, as written, is totally incompatible with current knowledge about pain management. Pain following surgery can largely be prevented by administering appropriate analgesics *before* surgery ('pre-emptive analgesia'), but pain that has become established after anaesthesia has worn off can only be controlled. This means that a literal interpretation of this article could result in animals being subjected to avoidable suffering, which is totally unacceptable.

Uncaged contend that the provisions above were breached in the course of Imutran's xenotransplantation research. In order to assess whether this is the case, and for a better understanding of what is meant by terms like 'severe' and 'substantial' we believe it is essential for the HO to explain more clearly how these terms are actually applied in practice within the legislation.

The cost-benefit assessment.

All applications to carry out research under the ASPA are subject to a cost-benefit assessment by the Secretary of State, in practice the HO Inspectorate. This means that in considering whether to grant a project licence for such work the Secretary of State:

> *"shall weigh the likely adverse effects on the animals concerned against the benefit likely to accrue as a result of the programme to be specified in the licence"* (ASPA, Section 5(4)).

The Chief Home Office Inspector set out the factors that are taken into account in this assessment in the APC annual report for 1997[32].

Uncaged's question recurring throughout its report is whether this cost-benefit assessment was done properly and with due regard given to animal suffering.

4.2 The project licences

The licensing process for research under the ASPA requires the prospective licensee who wishes to carry out the research to set out both the potential benefits and the harms of the proposed research within the project licence application form (see Appendix A). When reviewing the harms likely to be suffered, the full lifetime experience of each animal from birth to death should be taken into account. The Secretary of State (in practice as advised by the HO Inspectorate and the Animals Byelaws and Coroners Unit of the Home Office) must then make a judgement as to whether the research is a justified use of animals. In the case of the research reported here, the project licence applications would also have been submitted to the APC because they involved research of substantial severity on primates, some of whom were wild-caught. The APC Primate Sub-Committee would have reviewed the project licence applications first and they would then have gone to the full Committee for further consideration of the justification of the research.

A single project licence (number 80/848) covers most of the work in the leaked study reports i.e. the transplantation of transgenic hearts and kidneys from pigs into cynomolgous monkeys or baboons, followed by use of various immunosuppressant (or other) therapies to try to prolong the survival of the xenograft. There is a separate licence for the 3 studies on bone xenografts (80/1082) and there are a few studies looking at the effect of various immunosuppressants on untransplanted animals, again outside of the main project licence[33].

4.3 The research and the APC

There is very little reference to the APC in the Uncaged report or to the role of the Committee in assessing and monitoring this research. The Committee's annual reports however, refer to the discussions within the Committee. The relevant

paragraphs from the Committee's annual reports are reproduced below and summarise the APC's views to complete the picture of regulatory controls. UKXIRA also has some input, although assessing costs and benefits is not within the authority's remit. The inter-relationship between the APC, UKXIRA and the HO is important and is discussed in Section 4.4.

The initial project licence was considered by the APC in 1996 and the need for the Committee to keep fully appraised of the research was noted in the Committee's report for that year[34]:

> *"During 1996, the use of non-human primates in research directed towards xenotransplantation (specifically the transplantation of pig organs into humans) has formed a large part of the agenda of the Sub-committee. The speed of development of this work and its sensitivity makes it essential that the Sub-committee and, indeed, the full Committee keeps fully appraised of the progress of this work and its direction. It is also essential that the work is carefully and closely controlled. We accept that this will place extra regulatory burdens on those undertaking such work and that work may be delayed as a result. We do not apologise for this."*

In 1997, the APC saw material relating to this project on several occasions and reported as follows[35].

> *"On several occasions during the year, the Committee saw material relating to the use of wild-caught baboons in research relating to xenotrasplantation. A presentation was given to the Committee by the team leading this research in the UK outlining the objectives of the work, the progress made and future plans.*
>
> *A licence had been granted in 1996 for the study of immunosuppressive drug regimes. During 1996-97 it became clear that the pattern of animal use was not as expected when the authorities had initially been granted. We were satisfied that there had not been any infringements of the Act or of the licence conditions but, given that the work involved the use of wild-caught baboons, we needed to review these developments and closely monitor further work."*

At this time the APC felt that:

> "*the current project licence was too large to monitor properly and recommended that the licence holder be asked to consider splitting the work into more manageable projects, each with its own separate licence."*

In its report for 1998, the APC reported that[36]:

> "*During the year, two xenotransplantation applications came before the Committee. Both sought authority to transplant pig organs into primates in order to investigate the ability of the transplanted organ to support life, and to look at ways of preventing rejection and other adverse reactions.*
>
> *The first case involved the use of wild-caught primates in heart xenotransplantation research. The application sought authority to continue*

research started under a previous licence. It raised a number of difficult scientific and ethical issues, and the Committee decided to invite the research team to a meeting to explore some of these in detail."

The second application involved liver xenotransplantation. It raised many of the same issues as the heart application, and some new ones – in particular, the liver has much more complex physiological functions than the heart, so that the issue of whether any human patient could eventually benefit from transplantation of a pig liver was more complicated.

Following discussion with the research team, two separate licences were issued to Imutran in 1998 to cover the cardiac transplant work. There are no study reports for cardiac transplants after March 1997.

The APC advised that the liver transplant work was to be limited to a very small-scale pilot study. On receiving this advice the HO wrote to the applicant requesting confirmation that they still wished to pursue the application, but a reply was not received. (Note, this was not an Imutran project).

The main project licence expired and was renewed in 1999 and Dr Jennings saw and discussed this as a member of the APC. The application was submitted to the APC in March 1999[37]. The overall objective of the work was reported in the Committee's report for that year as:

"investigating immunosuppressive regimes for the control of pig kidneys transplanted into primates – macaques – with the ultimate objective of developing a regime that would allow transgenic pig kidneys to be used in cases of human renal failure".

The HO Inspectorate had required the applicant to make a number of modifications to the licence designed to reduce numbers of animals and levels of suffering and the APC itself made some recommendations in this respect (see below). The classification of the procedures within the project and the project itself were both topics of much discussion and the relevant paragraphs (31-35) from the subsequent APC report[37] are reproduced below.

"The applicants in this case had been engaged for some time, working for a commercial company, in investigating immunosuppressive regimes for the control of pig kidneys transplanted into primates – macaques – with the ultimate objective of developing a regime that would allow transgenic pig kidneys to be used in cases of human renal failure. This is work of potentially major significance for the future of human medicine. The applicants had been doing this work under a Home Office licence which was due to expire, and wished to continue the work.

The work did not, it seemed, involve any individual procedures whose severity would be regarded as substantial on their own. But the Home Office Inspectorate had concluded that the complete set of procedures as a whole did merit a 'substantial' rating. They would use relatively large numbers of both pigs and primates (100 primates and 200 pigs a year).

In line with our usual practice we first referred this application to our primate sub-committee. They made a number of suggestions aimed at reducing the number of macaques (and pigs) used in the work and the severity of the effects on them, and the applicants agreed to these. For instance, the applicants planned to allocate two pigs to each primate in case the first pig's kidneys were not suitable for transplantation. But if both pigs turned out to be unsuitable, it seemed that all three animals would be killed for no purpose. The Sub-committee argued, and the applicants accepted, that surgical work on the macaques should not begin until the piglet kidneys had been confirmed as suitable for transplant.

In the main Committee, we were concerned about why some of the individual procedures themselves did not merit a substantial rating (though we accepted that the Home Office Inspectorate had interpreted the rules properly). After much discussion we agreed, on balance, to advise the Home Secretary that the licence be granted. But we suggested to him that the licence should have conditions which would, among other things, minimise the number of animals used by ensuring clear accounting and justification in each case, with regular progress reports to the Inspectorate.

The Minister accepted our advice."

It is this project (pig to primate kidney transplantation) to which the Uncaged report refers in its criticism of the classification of the project as 'moderate' rather than 'substantial'. We understand that this classification reflects the Inspectorate's view that a moderate grading would allow earlier intervention if the effects on the animal were such that the severity banding was likely to be exceeded. RAD staff do not agree with this principle and would not have applied it in this case. We believe that projects involving procedures that, as a whole, merit a 'substantial' severity rating should be classified as such to alert the scientists and technicians involved to the need for greater vigilance, and in order to ensure a, meaningful, realistic and honest cost-benefit analysis. Furthermore, the classification and the criteria on which it is based, should be in the public domain so that the public and decision-makers in general can make informed judgements and decisions on ethical acceptability. We believe that a substantial classification was without doubt necessary for this project.

We are also concerned about the nature of the progress reports to the HO Inspectorate mentioned above. The only progress report contained in the leaked documents is a six monthly report which contains no reference whatsoever to the effects of procedures on the transplanted animals; instead it is purely concerned with xenograft survival times. We would ask whether this is normal for these sort of reports since we would have expected the condition of the animals to be reported, together with an ongoing assessment of how the actual costs compared to the predicted costs, and information about ongoing refinement measures.

The APC did not specify in its Annual Report for 1999 the information it expected to be provided in the *"regular progress reports"* to the Inspectorate or how frequent these reports should be. With hindsight we believe this should have been explicitly stated. We also seek clarification from the HO regarding the sort of ongoing information requested in projects of this type. A detailed ongoing review of actual suffering and opportunities for refinement, as well as progress with the research must

surely be essential as a pre-condition of licensing. The Chief Inspector, in his report, (para 5.19.1.) states that the reports *"were generally timely and informative. Further enquiries were at times necessary to elicit supplementary information or to verify the accuracy of the information supplied".* However, this does not tell us anything further about their content.

In the APC Report for 2000[38] the matter of the Uncaged Report is mentioned briefly with a note of the Committee's intention to discuss this further once the Chief Inspector's report became available. The report for 2001 is not yet available.

4.4 Inter-relation between the HO and the APC and UKXIRA

The APC is an independent statutory committee set up under Section 19 of the ASPA and as such its responsibilities relate to providing advice to the Secretary of State regarding work carried out under the ASPA, i.e. on the control of scientific procedures on animals that may cause them pain, suffering, distress or lasting harm. UKXIRA, on the other hand, has responsibility for providing a framework for regulating xenotransplantation[16]. This does not extend to regulation of the use of animals in preclinical research, which is the province of the HO and its Inspectorate, with additional input from the APC.

Clearly, there will be an overlap in the interests, if not in the responsibilities, of the APC, the HO and UKXIRA, but there will also be a conflict of interests. All three bodies recognise xenotransplantation as a matter of public concern. UKXIRA is required under its terms of reference to provide a process through which applications to undertake xenotransplantation in humans can be considered. As part of this process the Authority has had to indicate the type of information it would expect to be submitted in support of an application to proceed with clinical trials. Development of an appropriate proforma in this respect was one of the Authority's first tasks and this is reported in its Second Annual Report for 1998-1999[17]. UKXIRA, as with similar regulatory bodies in other countries will expect survival of animal organs/tissues to be demonstrated in higher primates before allowing clinical trials, but the Authority has not stated how long this survival period should be. Researchers therefore had no guidance about how long animals should be maintained in order to demonstrate efficacy and may have assumed that this should be as long 'as possible'. Note that the Food and Drug Administration (FDA) of the USA has only recently set a pre-clinical survival time of 6 months.

The ASPA requires that suffering should be of the minimum consistent with the aims of the experiment and for the shortest duration. The HO and the APC should be working to this principle. From the leaked study reports for the Imutran organ transplantation experiments it is obvious that maintaining animals with any decent quality of life, for even short periods of time, was extremely difficult. Therefore, the perceived or real need to demonstrate longer survival times, and obtain the maximum useful information from each animal's survival, directly conflicts with the desire, presumably of both the HO and the APC, to reduce endpoints. UKXIRA, however, did not see their role as setting time limits on survival and did not do so. Confidentiality issues between UKXIRA, APC and the HO with respect to the licences and the ongoing conduct of the research appear to have prevented all parties recognising these problems and responding to them.

Section 24 of the ASPA is concerned with the protection of confidential information. It states that: *"a person is guilty of an offence if otherwise than for the purpose of discharging his functions under this Act he discloses any information which has been obtained by him in the exercise of those functions and which he knows or has reasonable grounds for believing to have been given in confidence".* The requirement for confidentiality under the ASPA should surely not prevent committees set up specifically to advise the Government on related issues, from being party to and/or discussing the details of the issue they are advising on. We believe that this case, in particular, shows just how essential it is that there is communication and collaboration between committees so that each can make the most informed and appropriate decisions and act effectively to reduce animal suffering. We have stressed this point in RSPCA submissions to the APC Openness working group and the House of Lords Select Committee on Animals in Scientific Procedures.

We have also written to the Chairmen of the APC and UKXIRA about this matter and it has recently been agreed that a member of UKXIRA will be co-opted onto the APC primate sub-committee. This is an improvement, but still does not address the issue of confidentiality with respect to project licences and the ongoing monitoring of work carried out under them. Yet, for UKXIRA to be fully aware of the impact of xenotransplantation on animals, the Authority needs information regarding current research projects. At present, this is only possible if the project licence holders agree.

The need for a co-ordinated approach to the issue of xenotransplantation was stressed by the Kennedy Committee in 1997 in recommendations that were agreed by the Government at the time. Thus the Kennedy Committee recommendation para 74 and 9.9 states:

> *"We accordingly recommend that the National Standing Committee should act in co-ordination with the Animal Procedures Committee, and measures to achieve this (co-ordination) should be addressed as a matter of urgency".*

and in paras 73 and 9.8:

> *"We recommend that the Home Secretary treat xenotransplantation as a special case, and requests the APC to consider which mechanisms may be needed to deal in a co-ordinated manner with all applications which involve xenotransplantation."*

The Government replied thus:

> *"We recognise the need for the new UK Xenotransplantation Interim Regulatory Authority to work with the Home Office and the Animal Procedures Committee in order to prevent duplication and ensure that responsibilities are clear and understood."*

and

> *"Home Office Ministers will invite the Animal Procedures Committee to consider the ramifications of xenotransplantation for animal welfare. The mechanisms under which applications involving xenotransplantation are*

assessed and reviewed will be a matter which the Home Office will consider in liaison with the UK Xenotransplantation Interim Regulatory Authority".

It could probably be said that UKXIRA and the HO considered how applications are reviewed and assessed in the sense that UKXIRA clearly considers this to be the responsibility of the HO and the APC. But, have Ministers invited the APC to consider the ramifications of xenotransplantation for animal welfare? We cannot find reference to this in any of the APC reports in the four years since the Kennedy Committee report was published.

4.5 The cost - benefit assessment as a concept

As stated above the costs (harms) and likely benefits of all scientific procedures on animals must be assessed and weighed before a project is licensed. Judgements in this respect will always be subjective since they involve the weighing of disparate 'units' that cannot be objectively measured and compared. Moreover, different people will make different judgements depending on their own individual interpretation and assessment of the costs and benefits, and on their own interests and moral perspectives at the time[39]. The HO and the APC are both charged with having due regard to the interests of science and industry and with protecting animals from unnecessary suffering in experiments. This is difficult when the interests of science and industry will always conflict with those of the individual animals used. The HO's judgement is a statutory one; the APC's is advisory. The difficulty in deciding whether the judgements made by either or both authorities in this case were proper and fair, is that it is not clear how either term (costs or benefits) is defined and/or interpreted. Thus, to an individual animal no judgement to use that animal will be fair, because he/she will suffer to some degree (otherwise the experiment would not need licensing under the ASPA). Likewise, to an organisation concerned with the protection of animals, such as the RSPCA, no decision to cause animals pain, suffering, distress or lasting harm is likely to be considered fair.

The Chief HO Inspector outlined the HO thinking on the weighing of costs and benefits in a paper published in the APC Report for 1997[35] which is cited several times in the Uncaged report. The paper describes the factors that are taken into account by the HO Inspectorate when assessing costs and benefits, but does not really explain how this is done in practice. For example, project licence applicants proposing to use primates in experiments, and the Inspectorate in assessing such applications, are required to take into account the costs to the animals due to acquisition and transport[11,40]. It is not possible to tell, however, how these costs are weighted i.e. how significant they are considered to be. This difficulty with the cost-benefit assessment was highlighted in the RSPCA's submission to the APC's recent consultation on this issue, which is still in progress[41].

The Chief HO Inspector has also stated that the cost-benefit assessment is a 'process' not a single event. The difficulty of carrying out a cost-benefit assessment on the use of animals in individual research projects is widely recognised such that there are a number of papers setting out schemes to try to develop a better framework for decision making. It is also recognised that retrospective review of actual versus predicted costs and benefits can be very useful in further developing the process. Note that this is now part of the remit of the local ethical review processes (ERPs) set up under ASPA at all designated establishments[11], and the RAD believes retrospective

review is essential in order to help participants in the ERP develop their thinking on judgements relating to weighing costs and benefits.

A retrospective review (undertaken by the HO including the Inspectorate and the APC) of how the cost-benefit assessment was performed in this particular case, and in particular of the weighting that was given to the potential suffering of the animals concerned, would be very informative and is, we believe, essential. This would allow comparison of the predicted harms and benefits with those that actually occurred. It would help to assess the criticisms from Uncaged and the RSPCA in this specific case, and help inform future judgements on xenotransplantation and other areas of research. We are therefore astonished at the then Home Office Minister's response to the Chairman of the APC in his letter of April 2001[42] in which he states that *"a review based upon fresh information not available when the original assessments were carried out would have no relevance to the decisions reached at the time".* Clearly the Minister did not understand the valuable role such a review can have in developing decision-making, despite the fact that the ERP which the Government endorsed has this as part of its remit. We urge the present Minister to reconsider her predecessor's statement.

5. The cost-benefit assessment: costs to animals

In the following section, we review the comments made regarding the costs to animals by Uncaged and Imutran, and compare these with our own assessment of both.

5.1 The criticism of Imutran by Uncaged

Uncaged has criticised Imutran for not acknowledging that the primates used in these experiments suffered, for example as reported in the Daily Express article, 21 September 2000[2]. RAD has similar criticisms particularly with regard to some of the statements made in the company's response to the Uncaged report's allegations regarding animal suffering.

The statements that Imutran, or any company that carries out research on animals makes are important for a number of reasons. The project licence application form (Section 19b(vi)) requires that applicants set out a "*Description of the possible adverse effects, their likely incidence and proposed methods of prevention and control".* In order to do this and therefore fulfil his/her responsibilities under the ASPA the project licence applicant must be aware of the effects the research is likely to have on the animals involved. For this reason alone the comments Imutran make with respect to the animals they use in their research programme are important.

If Imutran recognises that animals suffer in their research but are not prepared to say so, then they are giving a misleading impression of the research that they do and their progress towards clinical application of organ xenotransplantation. If, on the other hand, they genuinely consider that the animals do not suffer, when in our opinion (given our expertise outlined in Part A, Section 2) they quite clearly do, then Imutran are failing in their responsibilities under the ASPA. How can they for example, possibly have accurately judged and described the harms to animals as they are required to do in a project licence application? The HO cannot then make a proper harm-benefit judgement and nor can the APC. Furthermore, if Imutran do not

consider the animals are suffering, then they are unlikely to recognise the need to provide appropriate care, nor will there be the motivation to seek to refine procedures to reduce suffering. Yet this is a direct responsibility of the project licence holder and others working under such a licence. Finally, whether or not Imutran consider the animals to suffer, the fact that they are reluctant to address this question demonstrates a remarkable lack of empathy for what the animals concerned experience.

In fact, evidence of any empathy for the animals they acquired and used is notably lacking in the leaked documents, until finally Imutran puts all the surgeries on hold because of the high numbers of 'technical failures' stating that *"Indeed, animal welfare is our concern and this issue must be addressed as a matter of urgency…"*.

5.2 RAD assessment of the harms suffered

The Uncaged report states that the primates used in the 39 xenotransplantation studies suffered a great deal and that this suffering was unjustified. In this section we will address the issue of whether suffering did in fact occur. However, we must point out that this is an unavoidable conclusion given the nature of the studies and their classification under ASPA as of moderate or substantial severity. The degree of suffering and whether this was adequately assessed is the more difficult question. The leaked documents that are particularly informative in this respect are: (a) the protocols of the draft study reports which describe how the animals were housed and cared for and how the experiments would be carried out; and (b) the clinical signs in the appendices to each study report which record twice daily observations of the animals.

Suffering encompasses psychological suffering in addition to physical pain caused as result of experimental procedures. Non-human primates are susceptible to both[43], and xenotransplantation research has great potential to cause both at every stage of the process from sourcing to ultimate euthanasia, although pain and/or suffering may not occur all the time, to every animal, and may vary in type and intensity.

As previously stated (Section 3.1), wild-caught baboons suffer the distress of capture from the wild and confinement in captivity. Both wild-caught baboons and captive-bred macaques have to endure the stress of removal from their social groups, of loading, and of long distance transport from their country of origin. The baboons used by Imutran, for example, endured a journey of 34 hours from their supply centre in Kenya to HLS[44]. Then there is the suffering involved with quarantine and acclimation to an unfamiliar laboratory environment, restrictive housing, social isolation, lack of environmental enrichment, the major surgery itself, post-operative recovery, the immunosuppressive regime, routine procedures, and the inevitable decline into illness due to transplant rejection and eventual death.

Thus, the suffering can be grouped broadly into that due to: (i) acquisition and transport; (ii) confinement in captivity; and (iii) the actual procedures and their effects.

5.2.1 Suffering due to acquisition and transport

The suffering due to acquisition and transport is described in Part B, Section 3 of this report, and in the RSPCA report Counting the Cost[22].

5.2.2 Suffering due to confinement in captivity

The Uncaged report identifies the "*primates' incarceration at HLS*" as a cost in terms of psychological suffering and deprivation. We agree with Uncaged, although we would apply this to primates in laboratories in general. The fact that it is difficult to satisfy these animals' psychological needs in a laboratory environment is just one reason why the RSPCA believes they should not be used in experiments.

The extent of the psychological suffering endured by the primates used at HLS by Imutran can be assessed by comparing the conditions for the primates described in the draft study reports with those factors considered essential by primatologists to provide for the psychological wellbeing (mental state) of captive primates. A good example of these are listed by the USA National Research Council's Institute of Laboratory Animal Research (ILAR)[43]. ILAR include detailed guidance on providing for psychological wellbeing through:

- housing that provides for suitable postural and locomotor expression;
- appropriate social companionship;
- opportunities to engage in behaviour related to foraging, exploration and other activities appropriate to the species, age, sex and condition of the animals (environmental enrichment);
- interactions with personnel that are generally positive and not a source of unnecessary stress.

In the following paragraphs, we consider each of these factors in turn in relation to the primates used at HLS by Imutran.

Housing
Adequate space is required for primates to express many aspects of their normal species–typical behavioural repertoire and to exercise. Cage space also determines whether there is sufficient room for suitable environmental enrichment. The primates used were confined in tiers of stainless steel and 'printboard' cages with crush back mechanisms. These met the requirements for cage size set out in the Home Office Code of Practice for Housing and Care of Animals Used in Scientific Procedures[45]. The problem is that the HO Codes of Practice[26,45] define minimum, not ideal, standards and as such these are insufficient to ensure that all the animals' physical and behavioural requirements are met. For example, whilst such cage sizes are sufficient for the primates to make postural adjustments, they can perform only very basic locomotor patterns (i.e. a few steps in any direction). The primates were confined in the cages for between 6 and 24 months. HLS acknowledge the ethical implications of confining primates (in this case, wild-caught baboons) in small cages in a letter sent in June 1999 to Imutran from HLS's Director of Toxicology which states "*we all have a responsibility to ensure that these animals do not spend unnecessary time in what must seem to be small enclosures*."

According to the study reports, the cages had grid floors, presumably because it was considered necessary to collect urine and faeces. The Home Office Code of Practice[26] says "*where grid floors are used the animals must have access to a suitable solid resting and foraging area*". We endorse this recommendation and consider a wholly gridded floor to be totally inappropriate.

Appropriate social companionship

In 1999, when Dr Jennings visited HLS, the stock baboons and macaques were group housed in large rooms or inter-connected gang cages. This is a significant welfare improvement on housing in standard laboratory caging. However, the protocols for the studies state that the experimental animals were singly-housed following transplant surgery. This was in order to facilitate accurate monitoring of individual food and water intake and urine and faeces output, and/or to prevent cage mates interfering with the wounds. Yet, we understand some animals were paired post transplant.

Single housing is in itself a cause of severe suffering for primates. Social interactions are considered to be one of the most important factors influencing their psychological wellbeing. A social environment enables primates to perform many species-appropriate behaviours including play, allo-grooming, allo-huddling, and sexual behaviour. Moreover, conspecifics contribute to meeting others' psychological needs by providing stimulation, environmental variation, challenge and opportunity for control. Both baboons and cynomolgus macaques are highly social animals who live in large troops. Their intense sociality means that they suffer greatly when separated from conspecifics for transport, quarantine and confinement for scientific procedures. The International Primatological Society (IPS)[27], the Primate Vaccine Evaluation Network (PVEN)[46], and the Berlin Workshop (an international workshop on the accommodation of laboratory animals in accordance with animal welfare requirements[47]) discuss contemporary scientific opinion on, and set out guidelines and recommendations for, the housing, husbandry and care of primates. All of these stress strongly that single housing of primates should be exceptional, should require special justification and should never be long-term.

Environmental enrichment

Environmental enrichment – provision of a stimulating environment which promotes expression of species-appropriate behavioural and mental activities - is essential for promoting psychological wellbeing in primates[43] (and many other animals). Where single housing is absolutely unavoidable, appropriate environmental enrichment (e.g. a varied diet provided in a variety of ways and cage furniture that encourages species-appropriate activities) is essential to buffer the stress and distress responses to social isolation and both the IPS and PVEN guidelines emphasise this.

The draft study reports make little reference to the provision of suitable environmental enrichment. For example, they state "W*holemeal bread and fresh fruit or vegetable produce was <u>sometimes</u> offered in order to enrich the environment and improve the interaction between animals and handlers*". This was in addition to the standard dry diet the animals received each morning. However, as noted by Uncaged, the reports do not indicate how often the bread, fruit and vegetables were offered, nor do they indicate whether these food items were varied at all or how they were presented. Some of the cynomolgus macaque studies mention a removable tray attached to the front half of each cage that contained wood chippings for use as a litter/forage substrate. Some mention a wooden perch, but no other cage additions. We have been advised that environmental enrichment was provided. This would have to have been considerably more than is described in the study reports, and provided for <u>all</u> individuals, otherwise in our view it would be woefully inadequate.

<u>*Conclusion*</u>

For a full and proper assessment of the conditions of housing and husbandry for the primates used at HLS by Imutran, we would need to know exactly what was provided for these animals at the time. Based on assessment of the information contained in the draft study reports and our observations of laboratory primate housing and husbandry, we consider that the conditions for the primates used in these studies were insufficient to meet their needs in terms of adequate space, social contact and environmental complexity, all of which are essential to provide for their psychological wellbeing. HLS, however, is by no means the only laboratory to which this criticism applies. The minimum standards in the existing HO Codes of Practice are, we believe, inadequate and out of date and require immediate revision.

Constraints of space and economic considerations seriously limit the size and complexity of the environment provided for primates in the vast majority of laboratories. We believe that if the needs of primates cannot be satisfied in the laboratory then, in a humane society, primates should not be used in laboratories at all. Financial costs should not be the deciding factor. In any case, pharmaceutical companies such as Novartis, the parent company of Imutran, make very large profits out of the products they develop using primates and other animals. We believe that a lot more of the money generated could be put back into animal facilities to reduce the suffering of the animals used and enhance their quality of life.

Interactions with personnel
Animal handling can also cause suffering if the personnel concerned do not understand the particular animals' needs and lack empathy with them. The Home Office Code of Practice for Housing and Care of Animals Used in Scientific Procedures[45] states that the least distressing method of handling primates is to train them to co-operate in routine procedures. In addition, the Code of Practice for the Housing and Care of Animals in Designated Breeding and Supplying Establishments[26] states that baboons are highly intelligent and can easily be trained to co-operate with staff.

The draft study reports, however, make no mention of training for the primates, although mention is made of food offered in addition to the standard dry diet to improve the interaction between the animals and their handlers. It may be that this is not the sort of matter that would be included in such reports. Macaques at HLS are currently trained to come to the front of the cage to be caught and handled for scientific procedures and RAD staff have observed this. However, we consider that there is a great deal more that could be done with socialisation, habituation and positive reinforcement training to reduce primate suffering and distress, and that all staff involved in primate use under the ASPA should receive adequate training in such matters. We would also ask whether the HO Inspectorate and the APC consider such questions when considering project licence applications involving the use of primates generally.

5.2.3 Suffering due to the procedures and their effects

The procedures reported in the majority of the study reports involve major abdominal surgery. This, by its very nature, will cause pain, suffering and distress – even if analgesia is administered. Tissue rejection and immunosuppressive treatment cause further suffering. It is for this reason that the research had to be licensed under the ASPA. The severity of the procedures and their effects was such that the initial

project licence was classified as of substantial severity, and there was serious debate over the moderate/substantial banding of the renewed licence. The HO Inspectorate and the APC therefore clearly considered that the animals would suffer[37]. In their response to the Uncaged report and in comments reported elsewhere, Imutran, however, seem either unwilling to acknowledge that the primates used suffered, or are ambivalent with regard to animal suffering. For example, in paragraphs 29 and 30 of their response it is recognised that xenotransplantation involves major surgical procedures, and that opening the abdominal cavity of a primate results in consequent trauma. However, Imutran also state (in paragraph 5) that the high frequency of "*animal quiet*", "*animal huddled*", and "*animal sitting at the front of the cage*" observations in the clinical signs to the study reports (highlighted by the Uncaged report as indicators of suffering) belong, in fact, to "*terminology normally used by non-human primate experts to describe normal looking healthy animals*".

We would disagree. Healthy primates in an appropriate state of wellbeing are characterised by a busy, confident manner, exhibit a wide range of the behavioural repertoire of their species, and are able to relax. *"Animal quiet"* is said by Imutran to be "*of no concern and corresponds to the attitude of a normal animal*". This may instead reflect listlessness due to illness, or apathy and withdrawal due to an under-stimulating environment. Impoverished laboratory environments commonly cause a state of long-term depression in primates characterised by hypoactivity, passivity and a lack of responsiveness to stimuli, and/or self-injury[48-57]. Cage size is also a factor as it relates to space for exercise and for enrichment, both of which are required to stimulate activity. Of course, "*animal sitting at the front of the cage*" is only normal if those particular individuals sitting at the front of the cage normally do so.

Imutran say *"animal huddled"* is a posture "*compatible with that of an animal in a resting/pre-sleeping position*". Whether this is actually the case depends on the exact definition of the word 'huddled' used by Imutran and the animal technicians reporting for the studies. Primatologists understand the words 'huddle' and 'huddling' to relate to either i) auto-huddling – a single animal hunching the body with back arched forwards so as to decrease the body surface area exposed and thereby minimise heat loss, or ii) allo-huddling – a number of animals crowding together in a hunched manner for thermoregulation and/or as an affiliative behaviour to derive comfort from tactile contact with others[58-68].

The fact that the animals were maintained singly and at temperatures between 19 and 25 ^{o}C, and that 'huddling' occurs most often in the clinical signs to the study reports in the days immediately after the transplant surgery and the days immediately preceding sacrifice on humane grounds, lends credence to the view that the posture observed by Imutran could in fact have been hunching over due to pain and not huddling at all. Wolfensohn and Lloyd[69], in a textbook on laboratory animal husbandry and care, state that in response to pain primates "*will have a miserable appearance, and may adopt a huddled position or crouch with head forwards and arms across the body*". It is at least as likely then that the posture adopted by the primates was indicative of pain, and not resting. In any case, it is not common place for healthy primates to rest in the presence of human technicians conducting thorough monitoring. In this regard, it is important to know how those monitoring the animals distinguished in the clinical signs lexicon or ethogram, between huddling as a posture adopted when resting or before sleep, and hunching over due to pain, and what specific training personnel had undergone with respect to primates before being given

the responsibility of monitoring such animals after major surgery. We discuss the issue of monitoring further in Section 8.2 of our report.

Even if these behaviours were not indicative of pain/suffering, other observations made in the clinical signs indicate that severe suffering occurred. Wolfensohn and Lloyd state that in primates "*acute abdominal pain may be shown by facial contortions, clenching of the teeth, restlessness and shaking*". The serious and very unpleasant effects listed in the study reports include grinding of the teeth, whole body shaking, infected wounds, wound-weeping, gangrene, haemorrhaging, weakness, vomiting, diarrhoea, abdominal and scrotal swelling and tremors.

It is a matter of extreme concern to the RSPCA that Imutran seem unaware of, or are unprepared to acknowledge, the indicators of suffering described in the clinical observations. This is despite the fact that a fundamental text book on laboratory husbandry and care lists the same signs as indicative of suffering and a cause for concern.

The video and surgeons notes

The animal recorded on the video supplied by Imutran had undergone an orthotopic heart transplant with subsequent treatment with the immunosuppressant mycophenalate. This experiment was carried out on six animals; five animals survived after Day 0. One animal, the baboon shown in the video, survived 39 days. This experiment was reported in the Journal of Heart and Lung Transplantation[70]. The reporting was criticised by the Uncaged report on the grounds that it implied the animal was in much better health than in fact he was[71].

The video footage of the individual baboon concerned, was taken on days 25 and 30 post transplant. RAD do not know if Imutran have any other video footage of this baboon or of any of the other transplanted primates. The video lasts for 2 minutes in total. On Day 25 the baboon was sitting on the floor of the animal room observing his conspecifics in their cages, moving around, and taking food from someone. His abdomen and lower back areas are shaved as are his forearms. The mid-ventral operation line of the baboon is clearly visible and looks well healed.

On Day 30 he is eating, then climbing the outside of the cages in the animal room and interacting with his conspecifics contained therein, i.e. emitting low, soft grunts (an affiliative vocalisation signalling friendly intentions) and presenting his chest in invitation of his conspecifics to groom him. These animals were singly-housed and were therefore likely to be desperate for social interaction. (Sensitivity to such behaviours, their meaning and implications for welfare are precisely the reason why technicians caring for primates must be well trained and why every establishment using primates should make arrangements for the provision of advice from a primatologist or ethologist with specific knowledge in primate behaviour). The clinical observation notes from the study reports on these days state the baboon was:

"*day 25: am - Alert and active. Dark faeces*
pm - Recovering from sedation
day 30: am - Quiet and huddled but alert if stimulated, sitting on perch, occasionally active.
pm – Unchanged"

The surgeon's notes for day 25 indicate that the baboon was taken to the operating room for debridement of the chest wound (mid-ventral operation line) which had been oozing serious matter intermittently since day 2 and had worsened since day 23.

During the 39 days post-operative period, the baboon is generally recorded as alert – and either quiet or active. He died from an acute cardiopulmonary decompensation immediately following administration of medication via oral gavage (according to the journal) and died following collapse (according to the study reports). One of the other animals on this study died prior to sacrifice on day 22. The other three animals were all killed for humane reasons between days 2 and 12.

Provision of the video allowed us to relate the clinical observation notes to the visible condition of the animals, albeit only one animal and the one that had survived for the longest time. Imutran were either not prepared or able to provide the surgeon's notes for the other animals. For an independent analysis of the suffering of these animals it would help to be able to compare similar footage of those that required euthanasia, alongside the surgeon's notes and clinical observations.

5.3 Costs: conclusions

Our conclusion is that these animals without doubt suffered, and we consider that it is wrong of Imutran not to acknowledge this more openly. As we stated previously, this cannot be in doubt because the research was classified as substantial and then moderate under ASPA. In Part 4 of the Uncaged report the author states that *"Perhaps the most significant aspect of the documentation that is the source of this report is the unparalleled insight it gives us into the fate of the animals who have been forced to endure xenotransplantation experiments. No longer is their suffering a source of conjecture or disputable".* This is entirely true and the information gained should be used to re-evaluate the cost-benefit judgements regarding xenotransplantation research and the technology as a whole.

There is a growing body of evidence from a wide variety of sources to show that animals whose wellbeing is compromised are often physiologically and immunologically abnormal and that experiments using them may reach unreliable conclusions[48,49]. Compounding the already severe suffering experienced due to the procedures and their effects by failing to satisfy the needs of the primates in terms of space, companionship and enrichment can only be detrimental to the research program, lessening its justification.

The questions remain as to whether the suffering of these animals was accurately predicted and assessed by the project licensee and how the predicted suffering was weighted. This requires access to the relevant section in the licence applications, which we do not have for the purposes of preparing this report. It is also necessary to consult the HO and the APC to hear how this was discussed at the time, and of course to hear from the project licensee, and others involved in the construction of the licence, how they identified and assessed animal suffering. We believe it is <u>essential</u> to further investigate these questions, particularly with respect to the comparison of predicted against the actual suffering, in order to inform future decisions. As a member of the APC, Dr Jennings will seek to take this forward.

With regard to the 1998 project licence, we would make the following comments. Section 19b(vi) of the project licence application requires applicants to set out a "*Description of the possible adverse effects, their likely incidence and proposed methods of prevention and control"*, or as it is written in the Guidance on the Operation of the ASPA, the project licence "*identifies the likely adverse effects, the means by which they will be avoided, recognised and alleviated*". We do not have a copy of the project licence application form for the experiments covered in the study reports (with the exception of part of the very last study), so it is not possible to assess whether the predicted adverse effects in the original licence were comparable to those actually seen and reported in the study reports. It may be difficult to predict adverse effects in completely new projects involving completely new procedures but this project licence was written with a great deal of experience of seeing and dealing with the adverse effects. Thus, the application to renew the licence should have been informed by the results of previous studies, and therefore would have been expected to accurately reflect the adverse effects previously seen in practice.

The details of this licence cannot be discussed here without breaching Section 24 of the Act. We therefore ask the APC and the HO to compare the effects recorded in the observation sheets in the study reports (using the renal transplants with immunosuppression) from work done under the original licence, with the predicted adverse effects outlined in the 19b reference number 2(vi) of the new licence to see if these correlate and if any useful information can be learned to inform future decisions.

We also ask what the mechanism is in general, and in this specific case, by which all those involved in drawing up and assessing licences (including the HO and the APC), and those carrying out and reporting on the work, can ensure the adverse effects are described as honestly and accurately as possible and with real empathy and understanding for what they mean for individual animals. We would seriously question whether this is adequately done.

6. The cost-benefit assessment: potential benefits

There are two points to consider: the benefits of xenotransplantation as a whole; and the benefits of Imutran's research covered in the 39 study reports and licensed under ASPA. The Uncaged report criticises xenotransplantation as being scientifically invalid, as well as ethically unacceptable, in both respects. If the Uncaged report's criticisms are correct and both the technology and the studies are scientifically invalid, then there would be no benefit to the research and it would therefore be unjustified under ASPA.

This is one of the arguments put forward by Uncaged as a basis for the criticism of the HO regarding the application of the cost-benefit assessment. The report alleges that the benefits were not properly assessed, (i.e., they were over-estimated) and did not take into account the criticisms of the technology as a whole (including matters such as the risk of transmission of zoonotic diseases to the wider population and the potential of alternative therapies).

6.1 Xenotransplantation as a technology

Xenotransplantation is primarily being developed as a means of overcoming the shortage of human organs for transplant. There is no doubt there is a shortfall in the numbers of human organs available and that there is an urgent need to overcome this problem. It is clear that if xenotransplantation is successful, safe and usable in the clinic then notwithstanding the moral concerns surrounding this use of animals, it would have great benefit to human patients.

It is very important to recognise that any research programme developing solutions to the urgent need for replacement human organs will inevitably cause animals to suffer. This includes the development of living organs cultured from cells or tissues, which will require animal tissues and serum and animals as recipients during preclinical trials. Even wholly artificial organs such as artificial hearts will be tested for biocompatibility and the ability to sustain life, which is generally done using sheep and calves. It can be argued that xenotransplantation is likely to cause the greatest suffering of all the techniques currently under development, due to the surgery and immunosuppressive regimes, and the large numbers of animals involved in the creation of transgenic pigs. The demand for organs that will sustain human life is not going to go away, however, and nor is the animal suffering associated with attempts to solve the human problem.

Once it has been decided that a goal like xenotransplantation is worth pursuing then this provides the impetus for a vast amount of research involving animals (including studies of efficacy, physiology, immunology, and infection risks) to be carried out on an international basis. Such research then tends to gather a momentum of its own regardless of the overall goal. Consideration of the full impact for animals has to take into account the nature of research carried out on an international basis.

RAD staff are well qualified to comment authoritatively on animal suffering and welfare. We do not, however, have the necessary expertise to undertake a critical analysis of the very many highly specific scientific questions surrounding xenotransplantation research. We cannot therefore attempt to make authoritative comments in the dispute over the benefits of xenotransplantation in general. To do so would be a considerable undertaking, requiring an in-depth review of the very extensive literature and current scientific thinking on this issue. This sort of review is normally the province of bodies such as the Nuffield Council on Bioethics, the Kennedy Committee, UKXIRA, and the Council of Europe Working Group on Xenotransplantation, the FDA in the USA and the World Health Organisation (WHO). In addition to reviewing the literature, such bodies require presentation and interviews with many of the experts in the various scientific fields involved. Note that the RAD strives to have a direct input into and otherwise influence such bodies with respect to raising the priority they give to animals and their welfare.

6.2 The Imutran projects

When considering how the cost-benefit assessment was carried out for the Imutran projects it is important to focus on the benefits that were perceived at the time of the application(s), given the information available from the existing state of knowledge, because this is what the projects would have been assessed against. When the original project was licensed in 1996, it was thought that clinical application of xenotransplantation was imminent. Indeed, this claim was made by Imutran and included in the preface to the Nuffield Council report. The technology was thus

widely considered to hold out great hope for overcoming the shortage of human organs. Both the Nuffield and Kennedy Committee reports agreed the potential benefits of the technology and considered these to be sufficiently significant to outweigh the costs to animals both as sources of organs and in research. They concluded that xenotransplantation was ethically acceptable in this respect. These views were formed after wide consultation within the scientific, medical, patient, religious and animal protection communities, and after consideration of factors including the level of risk of transmission of disease and of alternative approaches to solving the organ shortage. Similar views were expressed internationally. It was recognised however that proof of the potential benefit was required, and that this would necessitate research on animals including primates – this was highlighted as a concern by Dr Tony Suckling, Deputy Director General of the RSPCA (then Director of Scientific Affairs), who was a member of the Kennedy Committee.

The benefits of the Imutran research would have been assessed by both the HO and the APC, at least in part, on the basis of the above information, i.e. that there was an undisputed medical need for more organs, and that xenotransplantation was considered to have the potential to fulfil this need. Even if xenotransplantation was not successfully developed, the sort of research performed by Imutran would be likely to be considered to contribute to the understanding of immunology and organ rejection, and this too is highly likely to be considered sufficient benefit to justify the use of animals. Indeed, in 1999, when the initial project licence came to the APC for renewal, the APC stated that *"This is work of potentially major significance for the future of human medicine",* although this was a majority view, not a consensus[37]. The Chief Inspector likewise states in his report (para 3.2) that "*the Home Office judgement of 'potential benefit' was based upon the new scientific insights that might be gained*". Imutran did not advance, and the Home Office did not consider, claims of imminent clinical trials as a realistic short-term benefit.

It is now clear that Imutran's 1996 prediction was extraordinarily over-optimistic. The results of research by Imutran and others demonstrate that the expected progress towards clinical application of transplantation of animal organs into humans has just not been realised in the ensuing five years. Indeed, at the beginning of 2000, Novartis, the parent company, told Imutran that it was necessary to demonstrate long-term survival of transplanted organs within the ensuing 18 months if the research programme was to continue. UKXIRA, in the Authority's annual report for 2000 (para 6.15)[18], stated that "*It seems, therefore, that the likelihood of whole organ xenotransplantation (particularly for heart transplantation) being available within a clinically worthwhile time frame may be starting to recede".* We consider this to be an understatement. Likewise, the international xenotransplantation research community is now far less optimistic about the likely success of whole organ xenotransplantation, although the field of research seems to have developed its own self-perpetuating momentum with a vast amount of research being carried out and published worldwide. In addition, the technology is being applied to the development of cell therapies for conditions such as Parkinsons and Huntingdons disease and diabetes, where it is still considered to have a potentially useful application.

7. The cost-benefit assessment: was the research justified?

Given the shortage of human organs for transplants, we understand why this research was deemed to have potential benefit and was therefore considered to be justified at the time it was licensed, although from the perspective of an animal welfare organisation opposed to all experiments that cause pain, suffering or distress, and especially where primates are involved, we have great difficulty accepting this decision.

Subsequently, having read and assimilated the information on survival contained in the study reports, the RAD considers that in no way did the animals survive sufficiently well, with a sufficient quality of life post-transplant, for the transplant procedures to be considered successful. Hence, we do not consider that a significant and justifiable benefit was being achieved. The Chief Inspector states that the assessment of benefits was based on the scientific insights that might be gained from the research. We believe it is essential to ask what meaningful and useful information was obtained from these animals over the 7 years that the research was being conducted in the UK, when so many animals had to be euthanased so soon after transplantation?

We believe it is essential to address this point, together with the following questions, in order to inform future decision making with regard to authorisation and management of this sort of research, and to ensure transparency in how the overall process works:

- what were the intended aims of this research and were they (and therefore the benefits) compromised by the way the studies were designed and carried out?
- why was the poor survival of the animals used in this research not recognised and accepted as a problem earlier by the HO Inspectorate?
- why was the research programme not stopped by the HO before Imutran itself called a halt?
- what criteria are used to make such decisions, i.e. how much suffering to animals is allowed to occur, before a halt is called, what level of information gained justifies the continuation of the research?
- what is the mechanism for considering these questions and acting on subsequent decisions – how does this actually work in practice?
- what input does the APC have in monitoring such projects and what is the process for ensuring this is timely and meaningful?

We believe such questions are fundamental to the operation of the ASPA and should be addressed by the APC, the HO and the HO Inspectorate both independently and together.

8. Other issues relating to the study reports

8.1 Humane end-points and the inviolable termination condition

The severity limits, adverse effects and humane end-points of the experimental protocols must be detailed within each project licence. To describe these in a meaningful way, those constructing the project licence must be aware of the impact that the project will have on the animals at all stages from birth to death. Personnel involved in the animal work must be capable of health monitoring, be able to

recognise adverse effects and know what to do if end-points are approached. It is also a condition of the personal licence that if an animal is suffering severe pain which is not temporary and cannot be alleviated, s/he must be humanely killed at once, regardless of how important the animal is for the experiment; and the Secretary of State will not license any procedure likely to cause pain and distress that cannot be alleviated (see Part B, Section 4.1 of this report).

In studies of this sort we believe it is particularly important to define how an animal looks and behaves when approaching the end-point and for all involved to be familiar with the end-point and what to do when the animal reaches it. Nowhere in the draft protocols are the humane end-points of the studies described, although according to the report of the Chief Inspector detailed end-points were specified in the project licences. Some of the physiological parameters are written into some of the protocols in the study reports, (e.g. falling urine output, rising creatinine, listlessness and anorexia). These are however fairly minimally described and there is no indication of just how listless and anorexic an animal has to be before s/he is killed.

Staff monitoring the animals would have needed to know what the end-points were and how to recognise them, so they should have had access to the licences or to other information describing the end-points. At this distance in time, we cannot tell whether this was the case and whether all appropriate staff had access to sufficiently detailed information.

It is also not clear from the documents who had the responsibility of deciding that an animal should be humanely killed. The NVS or deputy NVS and the NACWO would normally be responsible for providing advice on the need to humanely kill an animal. However, in the protocols it states that the sponsor "*was contacted before any decision was taken to sacrifice an animal".* Again we cannot tell how this system operated in practice, but we are highlighting it as an issue of concern because the process of contacting the sponsor could take some time during which an animal causing concern would have continued to suffer.

The majority of the 39 studies, involving the deaths of 473 primates in total, seem to have very severe end-points in that two animals were found dead in their cage in the morning, presumably having died overnight, and many animals were euthanased for "*humane reasons*". Furthermore, the animals had, according to the clinical signs, been suffering for some days before euthanasia. The Uncaged report interprets this as a contravention of the provisions of ASPA relating to levels of allowable suffering and of the similar condition in EU law (see Section 4.1 of this report). Uncaged concluded, therefore, that not only did Imutran and HLS break the law but the HO were complicit in this, both in not stopping these experiments and in re-licensing HLS in 1997.

It is impossible to put a clear interpretation on the statements made in the Guidance notes to the ASPA regarding severe suffering without a better understanding of how the HO and the Inspectorate operate these critical points in practice. We are of course extremely concerned at the severity of the end-points used here and the length of time that suffering was endured. However, an allegation that the law has been broken cannot be substantiated without clarification of how statements regarding allowable levels of suffering are interpreted, and how they were applied in this particular case.

The Chief Inspector states in his report (para 5.14) that detailed end-points were specified in the project licences and that some required professional judgement in determining whether the end-point had been reached and on what action should be taken, whereas others did not. He also expressed the opinion that in *"several instances there was, in retrospect, sufficient evidence (as recorded in the original study documents) for irreversible renal failure to have been diagnosed up to 24 hours before the end-point was applied. I conclude that in these cases failure to implement the end-point earlier did result in some unnecessary animal suffering occurred as a result"*. We had come to the same conclusion from our reading of the 39 draft reports. The Chief Inspector however qualifies his statement by saying that this finding *"is a matter of clinical judgement"* which he offers as an opinion rather than an undisputed fact. He also states that *"the decisions that were taken by the surgical team were made in good faith and based upon their clinical experience and judgement"*. We believe their judgement was in serious error.

Clearly, it is totally unacceptable that endpoints were not properly interpreted and applied, with research that had the potential to cause substantial suffering. It is extremely distressing to think of animals suffering unnecessarily at such a level for a full twenty-four hours and this should be viewed as a serious infringement of the ASPA. We believe it is the responsibility of the Home Office to examine exactly how and why this happened and to report this to the APC, in order to try to minimise the occurrence of similar errors of judgement in the future.

8.2 Monitoring

In this section, the way adverse effects are monitored and the frequency of that monitoring is considered.

8.2.1 Monitoring adverse effects

Researchers using animals have statutory duties under the ASPA as well as moral duties to predict, recognise, assess and, as far as is possible, relieve any pain, or other adverse effect, suffered by their animals. It is a requirement that those carrying out procedures on animals should have had appropriate education and training, as should the NVS, NACWO and others working under the Act. There are no specific requirements for animal technicians looking after the animals but not performing procedures. We consider this to be wrong and that minimum qualifications should be set. The HO Inspectorate are expected to take into account the skills of the research team when assessing licence applications. However, it is the project licence holder, in this case within Imutran, who has ultimate responsibility for how the research is carried out.

We would expect this sort of study, involving primates, with their potential for increased suffering relative to other laboratory species[72], undergoing procedures classified by the HO Inspectorate as of moderate/substantial severity, to necessitate staff with an appropriate attitude and specific expertise in handling and caring for primates and in recognising adverse effects. There are both objective and subjective measures of an animal's condition that can be used for monitoring of adverse effects. The latter are particularly dependent on the expertise of the staff performing the monitoring, which in turn depends on training and experience. Those who know their charges well may be able to recognise when 'something is wrong' (i.e., an animal is

suffering adverse effects) and may be able to describe those effects in terms that can be used to guide others responsible for animal care. However, if staff have to make judgements in areas of research which are new to them, this may not always be possible. In general, only a knowledgeable, empathetic and alert observer can recognise changes in individual animals that are indicative of altered health and welfare particularly when the animals health is already compromised by surgery and immuno-suppression. It is thus imperative that those involved in primate use are trained to recognise and interpret both the normal behaviour (including social signalling systems) and abnormal behaviour of the species they are using and to understand the meaning and significance of these in terms of probable causes and their welfare, health and study implications. We consider the provision of advice from a primatologist or ethologist with special knowledge in primate behaviour to be particularly important here.

The study reports for the Imutran research make no mention of specialist training or the level of experience of staff. This might not be where such details would be written but how did the project licence holder satisfy himself/herself, as he/she is required to do, that HLS and Imutran's own staff had the necessary skills for the work that was to be carried out? Furthermore, the HO Inspectorate is presumably familiar with the staff at designated establishments, but how does the APC as the other source of advice to the Secretary of State, reassure itself about such matters?

8.2.2 Frequency of monitoring

Another concern is the frequency with which the animals were monitored throughout the xenotransplantation studies. Given that the animals had been subjected to major surgery and that organ rejection was a distinct possibility; given also the actual condition of the animals indicated by the study reports, and that so many of them were "*sacrificed for humane reasons*" – presumably meaning that the level of suffering necessitated euthanasia; we would expect for them to be routinely monitored during the 13 hour overnight period. In the study reports it states that recipient animals were closely monitored for the first 24 hours post transplant and thereafter checked regularly throughout the working day. The clinical sign sheets in the study reports only show two records, am and pm. However, both the Inspectorate and HLS staff say that animals were carefully monitored, with a frequency appropriate to their condition, and this was continued outside of normal working hours as and when appropriate. We understand that the laboratory day books (which were not part of the cache of leaked material) contained many more observation time points than the twice daily observations in the clinical records.

The study reports also state that the functioning of the xenograft was determined at least 3 times daily for the first 2 weeks, then twice daily, and a check of the general physical condition of each animal was performed at the same time. Thereafter xenograft function was checked more frequently at the discretion of the study director and/or HLS veterinary staff, but it is not clear whether these are the same observations as the checks referred to above, nor whether these observations were all confined to the working day. Some animals were found dead in the morning, presumably having died overnight, or were found dead in the afternoon. The Chief Inspector's report (para 5.13) states that: "*Records confirm that both veterinary and medical staff provided 24-hour-a-day clinical cover".* It is difficult to understand how, if this was the case, animals could be just 'found dead' in the morning.

8.3 End-points and monitoring: some key questions

The concerns and questions raised in Section 8 above can be summarised thus: were the animals monitored sufficiently closely, using parameters which would avoid prolonged and/or unnecessary suffering, with clearly defined end-points, by staff with sufficient expertise to do so? It is impossible for the RAD to ascertain this from the information available but the HO appear to consider the answer to all these questions to be yes. However, to be able to critically assess how the ASPA was applied in this case, and to make a judgement on whether animals regularly experienced avoidable suffering and thus, by inference, whether the law was or was not complied with, it is necessary to have access to detailed information on the following questions and points. For the public to have confidence in the regulatory process, such information needs to form part of a critical and independent review, which needs to take place within the public domain.

- Who decided when an animal had reached the end-point? We would expect this to be the NVS, but in the study reports it states that the sponsor must be contacted *"before any decision was taken to sacrifice an animal"*. How did this work in practice and who had the ultimate responsibility for the decision? If the sponsor had to be contacted, the efficacy of the system in practice is doubtful, as it seems that the condition of some animals on some studies could deteriorate very rapidly. Surely there would be no time to contact the sponsor, and in any case, waiting for their decision in such circumstances should constitute an infringement of the Act.

- What counted as a humane reason necessitating sacrifice of an animal?

- Did the project licence holder review the end-points in the light of clinical observations over the course of the study? How was this fed into subsequent licence applications?

- Instructions regarding the end-points and for monitoring the animals were not written into the protocols, nor do they appear in the project licence. Were these matters addressed elsewhere? We believe establishments should have formal, written, detailed instructions of the monitoring tasks to be performed. Lists of signs predictive of pain and suffering, and an effective recording scheme which indicates the action to be taken when certain combinations of signs occur, should be developed and disseminated to all those likely to need them. Details of any individual animals needing special attention should be kept in a designated, easily visible location and updated regularly.

- What factors are taken into account when monitoring animals on this sort of study? How long was each observation interval - how long is necessary to be able to properly assess individual animals? We believe that personnel should observe their animals with a frequency and duration appropriate to the severity level of each procedure, having due regard for circadian rhythms in activity. The presence of humans often affects animal behaviour and may be a stressor in some circumstances, so the potential conflict between the need to observe animals effectively and the animals' need for periods free from human contact should be recognised. Where procedures are severe and animals can deteriorate rapidly, as in the xenotransplantation research, some video monitoring may be necessary.

- Persons performing monitoring should be able to describe a variety of clinical and behavioural observations in an accurate, detailed, consistent and efficient manner - otherwise these might not prove useful in further decisions on the animals. This has obvious implications for animal welfare and for the quality of science.

- How did the Project licence holder and the HO Inspectorate assess staff competence?

- Do the HO and the APC consider these questions when reviewing licences?

Responsibility for deciding on matters such as end-points and monitoring would involve staff at Imutran and HLS, but Imutran must take ultimate responsibility because the project licence was theirs.

9. Surgical procedures and post-operative care

The HO takes into account the facilities and staffing when considering licence applications, and since this licence was granted, it must be assumed that both were thought to be satisfactory. How is competence to carry out the difficult procedures used in these studies measured - or is it assumed that because surgeons are surgeons their competence is guaranteed?

The Uncaged report criticises the HO decision, particularly in respect of the high 'technical failure rate' of surgical procedures. Imutran argue that there are several definitions of 'technical failure' and that the high technical failure rate was not necessarily as a result of problems with surgery. Nevertheless, the leaked papers from Imutran indicate that the company were having difficulty consistently finding sufficiently experienced surgeons to carry out the transplant operations and it is later acknowledged that this was the probable cause of some of the technical failures. The Chief Inspector subsequently states in his report (para 5.12.2) that "*The number of operative 'technical failures' (early graft failures not related to rejection) for the programme of a whole was of the order of 20% - consistent (and directly comparable) with reported rates in human paediatric practice. The incidence of technical failures varied from study to study, the available evidence does not indicate that the technical competence of any individual surgeon was sub-standard".*

We do not have enough information, (or the expertise) to decide on the competency or otherwise of the surgical team. However, the RAD considers that if technical failures were due to the inexperience or incompetence of the surgeons, then this is totally unacceptable. If surgeons fully experienced and competent in operating <u>on non-human primates</u> could not be guaranteed the research should not have gone ahead. We believe this issue should have been a justifiable reason for the HO and/or the APC to ask for the work to be suspended until the problem was rectified. However, despite the APC's clear desire to be kept informed of progress, and the fact that the Committee stressed the importance of regular progress reports to the Inspectorate, the Committee as a whole did not seem aware of the problem or at least this was not reported. Again, we believe it is important to ask how these sort of issues are normally handled by both the HO and the APC.

Since UKXIRA also has a direct interest in the success or failure of this research, we believe the Authority should have been made aware of these problems.

9.1 Errors in surgical procedures

Aside from the "technical failures" of the xenotransplantation procedures, there were two procedural errors highlighted by Uncaged. These were ascribed to HLS but in fact were the responsibility of the surgical team led by Imutran.

9.1.1 Surgical swab

During one transplantation procedure a surgical swab was left in an animal, who subsequently died from an infection. This error was the responsibility of the surgical team led by Imutran. Imutran acknowledged their responsibility stating that this incident was investigated at the time it occurred. They described the occurrence as a "*very regrettable one-off incidence that* [was] *the result of human error*", commenting that similar errors occasionally happen in human surgery.

According to the Chief Inspector's report (para 5.12.6) the situation arose because Imutran staff performed the operation without a trained theatre nurse present. The Chief Inspector describes this as an *"error of judgement"* by Imutran and that in his opinion *"this decision would not have been acceptable in clinical practice"*. We agree and consider this to be an extremely serious incident.

9.1.2 Frozen kidney

During one transplant operation, a pig kidney was inadvertently frozen rather than just being cooled, and this was only discovered once the recipient macaque had had his own kidney removed. The surgeon transplanted the kidney but the animal did not recover from the surgery. Again this was the responsibility of the Imutran surgical team. Imutran state that with hindsight the kidney should not have been used a decision with which the Chief Inspector (in his report para 5.12.7) concurs (note the Chief Inspector confirms that the kidney was not frozen solid but had evidence of surface frosting). Either way two lives were wasted. Mistakes can occur, but we would have expected that there would have been procedures in place to confirm the suitability of the kidney for transplant before the primate had his own kidney removed.

10. Matters relating to HLS

This section deals specifically with the allegations in the Uncaged report of errors at HLS in respect of the 16 conditions imposed on the establishment by the HO in 1997 as opposed to matters relating to the substance of the research itself, such as the severity of the procedures and the assessment of costs and benefits which are dealt with elsewhere in this report. We would like to stress that this section addresses HLS' compliance with regulations and legislation, rather than the nature of the xenotransplantation research, which has been dealt with earlier in this report.

10.1 Background material

The background material to the section of the Uncaged report dealing specifically with the conduct of the studies at HLS consists of the 39 study reports relating to the experiments, together with 30 documents, some of which are only partially legible. Many (18) of these latter documents do not appear critical of HLS. They include:

- Four, which relate to the contract between HLS and Imutran/ongoing work.
- One which relates to assessment of an alternative contractor.
- One set of Imutran meeting minutes – the relevance to HLS unclear.
- Two regarding standards in pathology at Papworth Hospital – no relevance to HLS.
- One regarding Imutran budgets – no relevance to HLS conduct.
- Two internal Imutran letters – no apparent relevance to HLS.
- One invoice to HLS – no relevance to HLS conduct.
- Two relating to Imutran's future research plans.
- Four relating to future need for studies to be regulatory compliant – these are only partially legible.

The documents from which Uncaged appear to have developed their criticisms of HLS are the 39 study reports themselves together with the following (12) documents:

- Two reports regarding inspection of HLS for Good Laboratory Practice (GLP) compliance by Imutran in early 1996.
- Two being an exchange of letters regarding late arrival of blood samples.
- Six dealing with an incident of re-use[93].
- Two relating to an error in drug administration and the incorrect timing of a blood sample[94].

The Uncaged report states that the documents represent *"evidence of manifold GLP shortfalls as well as undermining further the notion that HLS really did satisfy the sixteen conditions set by the Home Office"*. Uncaged therefore believes that HLS' certificate of designation under ASPA should be withdrawn.

We have carefully reviewed all the available information to see whether it is possible for us to establish whether HLS committed breaches of regulations (either ASPA or GLP[73]), which in the case of the ASPA would lead to withdrawal of its Certificate of Designation. Clearly the Chief Inspector, with the additional information available to him, does not consider such breaches occurred. Because of the serious nature of the allegations we have striven particularly hard to be objective in our review.

Part 4 of the Uncaged report gives a background to the situation in 1997 when a Channel 4 programme showing serious mistreatment of beagles at HLS resulted in a HO investigation. As a consequence at that time HLS was also inspected by the Department of Health's Good Laboratory Practice Management Authority (GLPMA) as a result of breaches in compliance with GLP. As a consequence of its investigation, the HO decided that in order for HLS to retain its position as a designated establishment it must comply with sixteen conditions designed to rectify the problems identified and to prevent their recurrence[34]. It was later announced that these conditions had been met and that a new certificate of designation had been issued. The RSPCA condemned the cruel treatment of the beagles at the time, and the Society was instrumental in ensuring the perpetrators were brought to trial. Some of the criticism in the Uncaged report relates to the period up to and including this

incident. The report goes on to state that the material on which it is based calls into question whether HLS have in fact complied with the 16 conditions imposed by the HO and whether in view of this, they should be allowed to continue to operate. This criticism is aimed at both HLS and the HO.

With regard to the criticisms relating to HLS, we have only reviewed information pertaining to the situation after the Channel 4 programme, once the sixteen conditions were said to be satisfied, since matters up to that date have already been dealt with by the relevant authorities and cannot therefore provide a basis on which to call for further action. There are therefore three issues to address, which separate into two categories relating to: i) GLP non-compliance and errors in data recording; and ii) errors with potential animal welfare consequences. These are dealt with separately below.

10.2 GLP non-compliance and errors in data recording

Uncaged's criticisms concerning GLP non-compliance and errors in data recording relate to problems that do not have a direct bearing on the suffering of animals used in the studies. Rather, our concern is that if good data was not obtained and not recorded, then the results of the experiments are useless and animals suffered in vain.

In this respect, we agree totally with the sentiment expressed in the Uncaged statement: "…*given the severe suffering inflicted on 120 higher primates* (referring to macaque studies) *in the course of these procedures the very least one can expect is for the studies to be conducted properly in order to ensure that the data is as reliable as possible."* We would apply this principle to all studies on all animals carried out in every establishment.

10.2.1 GLP non-compliance

Uncaged is concerned that HLS failed to comply with GLP requirements, thereby breaching GLP regulations and compromising the studies that were carried out. This would mean that the animals' lives, and the suffering they endured, were in effect 'wasted'. Imutran, however, state that i) the studies were 'exploratory' and would not normally be carried out to GLP standards; and ii) the studies were in any case not compromised. Both comments are correct for the following reasons.

The definition and application of GLP is often misunderstood. GLP is a quality assurance system developed largely for regulatory studies in, say, toxicity testing where data of a highly specific kind is generated for submission to a regulatory authority. From an animal welfare perspective, application of GLP can be detrimental. It is a very rigid system, which can prevent or delay changes that would benefit animals, such as the provision of environmental enrichment. The term 'Good Laboratory Practice' is therefore a misnomer as far as animals are concerned. It refers to technical standards, not standards of animal welfare, and RAD staff have found its rigid application often inhibits improved welfare (in toxicology, for example). Indeed, we would rather research and/or testing was not bound by such a rigid system and much of our work on environmental enrichment requires us to challenge the application of GLP.

It would be essential for HLS' work on regulatory toxicology to be GLP compliant. Breaches in this respect would be a serious matter, and this was a criticism in the Channel 4 programme. However, the xenotransplantation studies conducted at HLS were nowhere near being at a regulatory stage. Other parts of the study carried out elsewhere were not to GLP standards. At the time, it would not have been necessary for them to be carried out to GLP requirements because they were not conducted for submission to a regulatory authority, although the information would have been used to demonstrate efficacy.

Confusion on this issue has arisen for two reasons. Firstly, Imutran's Quality Systems Manager assessed HLS for GLP compliance in 1996 (prior to the Channel 4 programme) and reported this as unsatisfactory. However, Imutran and other companies often use GLP as a convenient baseline against which to measure the operating mechanisms and standards of companies to which they contract out work. This does not mean the standards have to be equal to GLP in order for work to be contracted-out to a company. In this case, Imutran says that it was differences in operating standards between HLS and themselves that were at issue, rather than actual GLP compliance. Secondly, subsequent comments by Imutran, in the documents reviewed, mention the need for GLP in respect of xenotransplantation studies. Determining whether the studies were to be conducted to GLP standards or not would have been a decision for Imutran which would have been dependant on the stage they were at in their research programme. Thus, later, in 1999, correspondence within Imutran indicates the company wanted to move to GLP compliant studies and data, possibly because they seemed closer to submitting survival data to the USA regulatory authorities. At this stage too, it was clear that UKXIRA would require xenotransplantation data to be generated to GLP standards.

In summary, the studies carried out at HLS did not have to comply with GLP and therefore GLP regulations were not contravened. The not inconsiderable concern of the RAD however, is that since Imutran had not required the studies to be GLP compliant because the experiments were exploratory, then if they ever reached the point where they wished to submit data to a regulatory authority, some of the studies might have had to be repeated using yet more animals. We believe it is important to know whether such questions are considered in the licensing process under ASPA.

10.2.2 Errors in data recording

The 39 study reports comprise a description of how each study was carried out and report the data collected from the animals used. Most of the data are presented as a series of tables. These included details of food and water intake, body weights, biochemical markers determined from blood samples and urine analysis, dosing levels, and organ weights. Each of the 39 studies, according to Imutran, have a total of approximately 5000 data points.

Throughout all the studies, there are places where points in the tables are recorded as 'NR', which is defined as *"not recorded in error"*. There are about 520 of these missing data points (about 0.25 % of the total for all 39 studies) which Uncaged claim calls the overall results of the research program into question. Imutran, however, state that the missing data points are not a problem, and that the missing data does not affect the outcome of the study. Without a great deal of scientific experience in assessing this kind of data, and without knowing exactly what Imutran were trying to

achieve from the studies, it is not possible for us to tell whether or not the missing data compromised the overall results, i.e., we do not know whether this is within the accepted 'norm' for experimental data of this sort. However, we do have information from one source that the auditors of GLP studies would be suspicious if errors of at least this level were not reported.

We also understand that NR is in fact a generic term and that there are a number of reasons why the data were not recorded. For example, an animal might not be well enough to weigh or take samples from (the condition of the animal is in itself a cause for considerable concern, but it is an acceptable reason for missing data); individual urine volumes could not be recorded from pair housed animals; some of the missing information is the responsibility of the surgical team led by Imutran. Some of the NRs may be due to mistakes but it is not possible to determine what percentage are the result of mistakes without going through the study reports with the person(s) at HLS and/or Imutran who kept the records.

To us '520 recording errors' seems a lot but the critical question is whether this lack of reporting represents poor management and an overall careless attitude at Imutran and HLS to the collection of data, and hence to the animals from which they came, or whether there were good reasons for these omissions, and finally whether it is likely to impact on the integrity of the study.

Without the relevant information with which to make a comparison, it is not possible to determine whether HLS or Imutran are any worse or any better than any other research establishment. We seek clarification on this point from the Home Office since this would help to build-up a picture of what standards are deemed acceptable. This would then give a minimum baseline against which to measure different establishments and hence from which to seek improvements.

10.3 Errors with potential animal welfare consequences

There were three errors in this category:

- a mistake in dosing level
- a mistake in sampling time;
- an incidence of reuse of a group of macaques.

10.3.1 An error in dose level and in sampling time

These two problems occurred in 1999. One animal was given four times the prescribed dose of an immunosuppressant, and a blood sample was taken at the wrong time (from the same animal in whom the swab had been left). According to the Chief Inspector (para 5.17.3 and 5.17.4) neither instance caused any unnecessary suffering and he states that, in the case of the drug overdose, the clinical records and post-mortem findings (to which RAD does not have access) *"strongly suggest that the animal's failing health was not due to drug toxicity"*. These mistakes were both clearly the responsibility of HLS. Both were very serious occurrences and were acknowledged as such at the time by HLS and subsequently by Imutran in their analysis of the Uncaged Report. Neither are likely to constitute an infringement of the ASPA, but we would nevertheless expect them to be reported to the Home Office and

for the Home Office to discuss the action necessary to ensure there was no possible repetition. We understand that this did in fact occur.

Although, according to the information available, these two errors appear to be isolated incidents, the concern again is that the system in place (and particularly for a study of this type causing substantial suffering to primates) allowed them to occur. Clearly, HLS management were themselves concerned and instigated a re-organisation in management and reporting lines, according to a letter written by HLS to Imutran. It is not known whether there was any other reason for this action.

10.3.2 Re-use, an infringement of ASPA

Under the ASPA no animal may be used for more than one procedure unless the second procedure is carried out under terminal anaesthesia where the animal is killed at the end. There are exceptions to this rule, where it is considered that reuse of an individual animal would not cause additional suffering, and would be preferable to using an additional animal. Such exceptions must be authorised by the HO and unauthorised re-use is an infringement of the Act. We understand that a single infringement such as this would not normally be considered by the Home Office to be grounds for removal of a Certificate of Designation: we believe that the Home Office's policy on this matter should be available to public scrutiny.

The leaked material shows that a group of macaques was reused in a second procedure. The concern expressed in the Uncaged report is that the management and communication system at HLS at the time allowed this reuse to occur, and that therefore the sixteen conditions designed to rectify the problems identified at HLS following the Channel 4 programme could not have been properly satisfied. The incident was self-reported by HLS to the HO. The re-use consisted of the administration of prophylactic drugs to reduce the risk of anaemia following surgery – the mistake was realised before the surgery took place. The Chief Inspector (see his para 5.6.1 and 5.6.2) states that this incident was dealt with as a formal infringement at the time and that no significant unnecessary animal suffering resulted.

The RSPCA considers that the unauthorised use of any animal in a scientific procedure, and in particular a primate, is unacceptable and that there should always be appropriate systems in place to ensure that this cannot happen.

10.4 Summary points

The RSPCA considers infringements of the ASPA and mistakes that give rise to additional animal welfare problems to be a very serious matter and that adequate training, management and supervisory structures must be in place to prevent these happening. This was clearly not the case in the instances described above but, nevertheless, this is insufficient evidence on which to base a claim that the 16 conditions imposed on HLS in 1997 had not been satisfied. The point at issue is really whether, as Imutran state, these incidents (and the two which were the responsibility of Imutran), which took place over the 4 year period covered by the report are "*regrettable one off instances that were the result of human error*" or whether they represent a careless attitude within both companies to the studies and to the animals involved. It is just not possible to ascertain this from the information available in the documents available to us.

If there is to be any confidence in the way the ASPA is implemented and the sanctions that are applied when infringements occur, then it is important for the action taken in such cases to be meaningful and effective and widely and clearly reported. What we really need to know from the HO in order to assess how effective sanctions such as those applied to HLS are, is how many mistakes of this nature would be allowed to happen before work under the project licence would be stopped? What level of compliance does the HO, or for that matter, the APC, expect? The HO has published guidance on how infringements are assessed and the actions they take in response, but this guidance does not answer these questions and nor does the Chief Inspector's report.

11. Primates as a biohazard

The Uncaged report draws attention to the fact that there is a degree of health risk to humans in working with animals, particularly wild-caught primates. This risk is not, of course, confined to work on laboratory animals. As a consequence, there are extensive regulations addressing this issue, for example in relation to the way animals are housed, handled and transported, and their tissues handled, transported and stored. The Uncaged report suggests such regulations may have been breached and that this may have put patients at hospitals where surgeons who carried out the xenotransplantation procedures were working, and/or the public, at risk from pathogens that may have been present in the animals.

In order to say whether any of these regulations had been breached and whether there had been any risk to public health as a result, it is necessary to have a detailed knowledge of the relevant regulations, and far more information with respect to the procedures at Imutran, HLS, and the hospitals where the surgeons worked and where some of the tissue samples were analysed, than is available from the information leaked from Imutran. This issue does not have a bearing on the operation of the ASPA and is outside the RAD's area of expertise. We cannot therefore comment further on this matter.

12. Summary of main concerns

The main concerns and questions raised throughout this report, both with regard to xenotransplantation as a whole and to the specific research carried out under the ASPA fall into three main categories; the implementation of and compliance with the ASPA (section 12.1); primate issues (12.2); and xenotransplantation as a technology (12.3).

12.1 The ASPA: implementation and compliance

We have identified a number of fundamental issues and concerns with respect to the way current regulations and associated controls, and the decision-making processes within the regulatory system as a whole, operate. We are especially concerned with how the specific requirements of ASPA and its associated codes of practice are actually interpreted on the ground by everyone involved – from the regulatory authorities to those designing studies and carrying out the research. Note that

although xenotransplantation and the trade in, and experimental use of, primates is the specific case addressed here, similar concerns can also be extended to the use of animals in research and testing in general.

Any analysis of the sort we have attempted is hampered by the confidentiality required by the ASPA, and in this specific case, by the injunction. This means that we have limited access to the information necessary for a comprehensive review. Even where Dr Jennings has more information by virtue of membership of both APC and UKXIRA, this information could not be used in this report even where it provides satisfactory answers to some of our questions. The Chief Inspector's report, though welcome in its assurances of regulatory compliance, is limited in the information it provides and does not help with our more fundamental questions about how standards are assessed and decisions made.

If there is to be confidence in the way the ASPA is implemented (and particularly in the sanctions that are applied when infringements occur) then it is important for far more information to be in the public domain, and for there to be greater transparency about the whole process of how research is conducted. We have summarised below some of the questions we believe are important in helping to ensure greater transparency of the decision making process under ASPA. As stated previously (Part A Section 5) we have already discussed, in confidence, some of the individual questions which underlie the points summarised below (particularly those regarding decisions on end-points, monitoring of animals, and staff training and expertise) with the Chief Inspector, HLS staff, and within the APC. But we believe they should all be answered in the public domain, and be subjected to in-depth discussion.

- What level of compliance with ASPA is expected by the HO, or for that matter, the APC? The HO has published guidance on how infringements are assessed and the actions it takes in response, but this guidance does not answer these questions and nor does the Chief Inspector's report.

- How are the severity limits of protocols and projects, the inviolable termination condition in the personal licence, and the statement on p32 of the Guidance notes on the operation of ASPA that the Secretary of State will not license any procedure likely to cause severe pain, suffering, or distress that cannot be alleviated, interpreted in practice in the case of research that is by its nature highly likely to cause severe suffering?

- Why was the poor survival of the animals used in this research not recognised and accepted as a problem earlier by the HO Inspectorate?

- Why was the research programme not stopped by the HO before Imutran itself called a halt?

- What criteria are used to make such decisions, i.e. how unsuccessful would a project have to be (or how little information would it have to yield), and how much suffering to animals would be allowed to occur, before a halt would be called?

- What is the mechanism for considering these questions and acting on subsequent decisions – how does this actually work in practice?

- What input does the APC have into the initial project assessment and to monitoring such projects?

- What sort of information does the APC then expect to be provided with when requesting feedback on projects with which it is concerned?

- Does the APC carry out a retrospective review of the projects it has reviewed; and what is the process for ensuring that this work is timely and meaningful?

12.1.1 Assessing costs and benefits

It is a matter of extreme concern to the RSPCA that Imutran seems unaware of, or is unprepared to acknowledge, the indicators of potential suffering listed in the clinical observations. This is despite the fact that a fundamental textbook on laboratory husbandry and care lists these same indicators as possible signs of suffering and a definite cause for concern.

There are also the questions of whether the suffering of the animals was accurately predicted and assessed and how the predicted suffering was weighted in the project licence applications. These require access to the relevant section in the licence applications and consultation with the HO and the APC.

- We believe it is <u>essential</u> to further investigate both of these questions - relating predicted against actual suffering - in order to inform future decisions. This would be particularly informative since the results of research carried out under the initial project licence should have been used to inform subsequent applications. The details of the licences cannot be discussed here without breaching Section 24 of the Act. We therefore ask the APC and the HO to compare the effects recorded in the observation sheets in the study reports (using the renal transplants with immunosuppression) from work done under the original licence, with the <u>predicted</u> adverse effects outlined in the 19b reference number 2(vi) of the new licence.

- What is the mechanism (in general, and in this specific case), by which all those involved in drawing up licences (including the HO and the APC), and those carrying out and reporting on the work, <u>can ensure the adverse effects are described as honestly and accurately as possible and with real empathy and understanding for what they mean for individual animals</u>?

12.1.2 Humane end-points and monitoring of animals

Clearly defined end-points, together with efficient monitoring of animals, are crucial for accurate assessment of the level and nature of animal suffering, and hence for ensuring that suffering is kept to the absolute minimum as required under the project licence. We believe that establishments should have formal, written, detailed instructions of the monitoring tasks to be performed and records of these should be maintained. Lists of signs predictive of pain and suffering, and an effective recording scheme which indicates the action to be taken when certain combinations of signs

occur, should be developed and disseminated, and training in their use provided, to all those likely to need them. Details of any individual animals needing special attention should be kept in a designated, easily visible location and updated regularly.

It is not possible to ascertain exactly what was done with regard to end-points and monitoring of animals in the studies reported here from the information available. We are seriously concerned, however, that in some studies the primates were apparently not monitored sufficiently closely, using parameters sufficient to avoid prolonged and/or unnecessary suffering. It is totally unacceptable that some animals appear to have suffered for 24 hours longer than necessary. For these concerns to be addressed, as we believe they must, and to critically assess how the ASPA was applied in this case, it is necessary to know:

- How were the end-points decided and described in the project licence and how were these implemented in practice? For example, who decided when an animal had reached the end-point? We would expect this to be the NVS in consultation with other animal care staff, but in the study reports it states that the sponsor must be contacted *"before any decision was taken to sacrifice an animal"*. How did this work in practice and who had the ultimate responsibility for the decision? If the sponsor had to be contacted, the efficacy of the system in practice is doubtful, as it seems that the condition of some animals on some studies could deteriorate very rapidly. Surely there would be no time to contact the sponsor, and in any case, waiting for their decision in such circumstances should constitute an infringement of the Act.

- What counted as a humane reason necessitating sacrifice of an animal?

- Were the end-points reviewed in the light of clinical observations over the course of the study? How were the findings incorporated into subsequent licence applications?

- How were factors such as the monitoring interval and indicators of suffering defined and documented and who was involved in these decisions - the project licence holder and/or surgeons (i.e. Imutran), HLS staff, e.g., NVS, NACWO, the study director; the HO Inspectorate; or all of these?

- How often were the animals monitored outside of checking the functioning of the xenograft or are these one and the same, e.g., twice, three, ten times daily? What did this monitoring entail? How long was each observation interval - how long is necessary to be able to properly assess individual animals?

- What kind of training do staff monitoring animals on these type of studies have? How is competence assessed?

- Do the HO and the APC consider all of these questions when reviewing licences?

12.1.3 Severity bandings

Some of the research reported in the 39 draft study reports clearly involved substantial suffering by the definitions in the Guidance Notes to the Operation of the ASPA.

- We believe that projects involving procedures that, as a whole, merit a substantial severity rating should be classified as such to alert the scientists and technicians involved to the need for greater vigilance.

It is also important in order to develop cost-benefit assessments and ethical decision making to know how many animals within a project actually experience substantial suffering. This sort of information should be reported to the APC primate sub-committee and also needs to be included in the annual HO Statistics for all species.

- We urge the HO fully to consider ways of presenting this information in the Annual Statistics of Scientific Procedures on Living Animals.

12.1.4 Retrospective review

A retrospective review (undertaken by the HO and the APC) of how the cost-benefit assessment under the ASPA was performed in this particular case, and in particular of the weighting that was given to the potential suffering of the animals concerned, would be very informative and in our view is absolutely essential. This would allow comparison of the predicted harms and benefits with those that actually occurred. It would help to assess the criticisms from Uncaged and the RSPCA in this specific case, and help inform future judgements on xenotransplantation and other areas of research. It could also help develop a constructive approach to the retrospective review, which is now a requirement of the local ethical review process.

We are therefore astonished at the then Home Office Minister's response to the Chairman of the APC in his letter of April 2001 in which he states that *"a review based upon fresh information not available when the original assessments were carried out would have no relevance to the decisions reached at the time"*. Clearly the Minister did not understand the valuable role such a review can have in developing decision-making, despite the fact that the ERP which the Government endorsed, has this as part of its remit.

- We urge the present Minister to reconsider her predecessor's statement and support a full and retrospective review.

- We ask the APC to do this in any event.

12.1.5 Surgical technique

We do not have enough information or expertise to decide on the competency or otherwise of the surgical team. However, the RAD considers that if technical failures were due to the inexperience, incompetence, or unavailability of the surgeons, then this is totally unacceptable. If surgeons fully experienced and competent in operating on non-human primates could not be guaranteed the research should not have gone ahead. This should have been a justifiable reason for the HO and/or the APC to ask for the work to be suspended until the problem was rectified.

Despite the APC's stated desire to be kept informed of progress, and the fact that the Committee stressed the importance of regular progress reports to the Inspectorate, the Committee as a whole did not seem aware of the problem or at least this was not reported.

- We ask for more information on how these sort of issues are normally handled by both the HO and the APC.

12.1.6 GLP and other 'errors'

The RSPCA considers infringements of the ASPA, and mistakes that give rise to additional animal welfare problems such as described in Section 10 of this report, to be very serious matters. Adequate training, management and supervisory structures should help to prevent these occurring but were insufficient in the instances described above. Nevertheless, this is insufficient evidence on which to base a claim that the 16 conditions imposed on HLS in 1997 had not been satisfied, especially since at least two of the five incidents (the surgical swab and the 'frozen' kidney) are the direct responsibility of Imutran, not HLS.

The point at issue is really whether, as Imutran states, these incidents which took place over the 4 year period covered by the report are each "*regrettable one off instances that were the result of human error*" or whether they represent a careless attitude within both companies to the studies and to the animals involved. It is just not possible to ascertain this at this distance in time and from the information in the documents available to us, but if the errors result from a careless attitude then this is clearly absolutely unacceptable.

GLP
The studies carried out at HLS did not have to comply with GLP because they were exploratory and therefore the criticism of HLS's GLP standards are not sustainable. Our concern, however, is that if Imutran ever reached the point where they wished to submit data to a regulatory authority, some of the studies might have had to be repeated using yet more animals.

- We believe it is important to know whether such questions are considered in the licensing process under ASPA by the applicants, the HO and the APC.

Data errors
A further critical question with regard to the data 'reporting errors' is whether there were good reasons for the missing data points (as there clearly were in some instances) or whether this lack of reporting represents poor management and an overall lack of care at Imutran and HLS with respect to the collection of data, and hence for the animals from which they came. Imutran state that the 'reporting errors' did not compromise the integrity of the studies and we are not in a position to judge this, nor to determine whether HLS or Imutran are any worse or any better than any other research establishment or organisation in this respect.

- We believe it is important to seek clarification on this point from the Home Office since this would help to build-up a picture of what standards are deemed acceptable. This would then give a minimum baseline against which to measure different establishments and hence from which to seek improvements.

Re-use
The RSPCA considers that the unauthorised re-use of any animal in a scientific procedure, and in particular a primate, is unacceptable. We recognise that in this case

the re-use was self-reported and dealt with by the HO and the APC. Nevertheless there should always be appropriate systems in place to ensure that this cannot happen.

- We ask the HO to clarify whether it is confident that HLS now has a system in place to ensure that unauthorised re-use does not occur.

In order to assess how effective the ASPA is in preventing all the types of error highlighted above from occurring more widely, it is necessary to ascertain how many mistakes of this nature would be allowed to happen before work under the project licence would have been stopped.

- We ask the HO what levels of error in (i) surgical practice, (ii) data gathering and (iii) unauthorised re-use it would consider to be acceptable, and at what point it would halt a programme of research.

12.1.7 Confidentiality between APC, UKXIRA and the HO

There is an overlap in the interests, if not in the responsibilities, of the APC, the HO and UKXIRA. There is also likely to be some conflict of interests since UKXIRA will need to see long term survival of transplanted primates before authorising clinical trials, yet the HO and APC will want to ensure the suffering of the primates used is kept to a minimum.

We believe that confidentiality with respect to the project licences and the ongoing conduct of this research prevented all parties i.e. UKXIRA, APC and the HO recognising and responding to some of the problems and issues outlined in our report. There is a need for far greater collaboration, co-ordination and openness where there are a number of bodies responsible for initiating, regulating and monitoring a field of research, to ensure that any problems are addressed quickly and efficiently.

- The issue of confidentiality and cross-committee co-ordination must be addressed by UKXIRA, APC and the HO. It is, however, a specific example of the general issues being considered by the Government with respect to the Freedom of Information bill and Section 24 of ASPA. We would therefore urge that this issue be considered as part of that process as well.

12.2 Primate issues

12.2.1 Primate acquisition and transport

The RSPCA believes the whole issue of primate acquisition and transport needs to be urgently re-evaluated by those with responsibilities for regulating it, and action must be taken by the HO and DEFRA to improve primate welfare. The Society's recommendations in this respect are set out in a detailed report on the primate trade[29].

The issue of HO inspection of overseas breeding and supplying centres is a particular concern. It seems extraordinary that, given the additional 'protection' granted to primates by the ASPA, all facilities supplying them are not regularly inspected.

- We understand the APC Primate Sub-Committee has sourcing of primates in its work programme and we seek assurance that the issue of inspection of overseas centres is addressed as a matter of urgency.

- The number of HO Inspectors is now being increased to 33. We believe that regular visits to overseas primate suppliers should be an essential part of their work programme for as long as primate imports continue and seek assurance from the HO that this will be the case.

Responsibility for primate welfare does not, however, just lie with the regulating authorities. For primate suffering to be reduced, it is essential that all involved with primate use are aware of all the stresses imposed on the animals. It is therefore incumbent upon project licence holders, ethical review processes, regulatory and funding bodies to take greater responsibility for the primates used by or for them. They must ensure that they are fully aware of, and give due consideration to, all of the costs to the primates involved, including those due to acquisition and transport.

- All those involved with primate use, directly or indirectly, must strive to ensure the highest standards of welfare for the primate concerned at all stages of acquisition and transport and actively consider what additional pressure they can exert on breeding and supplying establishments to raise their standards.

There is also the question of whether UK scientists and/or institutions should be allowed to use suppliers that do not meet UK standards for all their animals, in order to enable responsible users and the HO to exert what influence they can to improve standards, or should such overseas suppliers be disallowed altogether, regardless of whether there is an alternative source? The consequences of any action regarding the sourcing of primates from overseas must be fully evaluated before any decisions are made in order to ensure that the best outcome for the animals is secured.

- We urge the APC to consider in depth ways in which overseas primate breeders and suppliers could be influenced to improve both standards and attitudes, paying full regard to the long-term welfare consequences engendered by any such actions.

12.2.2 Primate husbandry

It is our view, based on assessment of the information contained in the study reports, and our observations of laboratory animal husbandry, that the conditions for the experimental primates confined at HLS were insufficient to meet their needs in terms of adequate space, social contact and environmental complexity, all of which are essential to provide for their psychological wellbeing. HLS, however, is not the only laboratory to which this applies. Constraints of space, the nature of studies, and economic considerations seriously limit the quality and quantity of the environment provided in any laboratory. However, we believe that if the needs of primates cannot be satisfied in the laboratory then, in a humane society, primates should not be used in laboratories at all. Financial costs should not be the deciding factor. Pharmaceutical companies such as Novartis, the parent company of Imutran, make very large profits out of the products they develop using animals. Therefore:

- We believe that a lot more of the profits generated by pharmaceutical companies should be put back into animal facilities to enhance the quality of life, and reduce the suffering, of the animals such companies depend upon.

It is said that the public accept the use of animals for 'important medical purposes'. However, this is with the proviso that animals are treated humanely. Humane treatment of animals requires that animals be viewed as individuals, not just as a renewable resource. Their use and care should reflect this.

- Instead of complaining about the expense and bureaucracy of UK legislation, the pharmaceutical industry should embrace the spirit of this legislation and give animals and their welfare higher priority – whether this is in their own in-house facilities or in the facilities to which they contract out their work.

Finally we consider the HO Codes of Practice on laboratory animals to be out of date and urgently in need of revision.

- We urge the HO to initiate a complete review of the current minimum standards for primate husbandry and care and to revise these to better take account of current knowledge of the psychological and behavioural needs of these animals.

12.2.3 Training of primates and of staff to work with them

The need for training of primates in order to facilitate procedures and therefore reduce associated suffering wherever possible is generally recognised but there is no evidence that this was integral to Imutran's research programme or HLS' procedures at the time.

- We seek confirmation from Imutran, HLS, the HO and APC that the need for training for primates is well documented, and that all staff involved in primate use receive adequate training in such matters.

How did the project licence holder satisfy himself, as he/she is required to do, that HLS and Imutran's own staff had the necessary skills? The HO Inspectorate is presumably familiar with the staff at designated establishments, but how does the APC as the other source of advice to the Secretary of State reassure itself about such matters?

- We also ask whether the HO Inspectorate and the APC consider the training of staff when reviewing project licence applications involving the use of primates generally.

12.3 Xenotransplantation as a technology

The Kennedy Committee report stated that the ethical acceptability of xenotransplantation depended on the full evaluation of its costs and benefits and it emphasized that such assessments are not 'one off'. We do not believe that the harms to animals of xenotransplantation 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 harms have not been adequately assessed in the overall harm/benefit assessment of

xenotransplantation (note, this is outside of the specific cost/benefit assessment required under the ASPA). The 'costs' to animals both as sources of xenografts, and in particular in the associated research, are unquestionably extremely high. Furthermore, we believe the benefits of the technology, at least as applied to solid organs have not been realized and are increasingly unlikely to be. Thus:

- it is not clear what meaningful and useful information was obtained from the animals used in the Imutran studies when so many had to be euthanased. What were the specific aims of this research and was it expected to advance xenotransplantation towards clinical use? Were these aims (and therefore the benefits) compromised by the way the studies were carried out?

We believe that a stringent and critical re-evaluation of this issue is long overdue. However, 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. We therefore believe it imperative that information regarding the full impact of xenotransplantation research on the animals concerned should be in the public domain, otherwise people cannot make a fully informed judgement on whether they believe the development of xenotransplantation to be morally 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 clearly necessary. This must however apply to all interested parties including animal protection groups.

We believe UKXIRA should consider this issue as a matter of urgency as part of its terms of reference which are 'to provide a focal point on xenotransplantation issues within government'. In so doing, the Authority should:

- review the recommendations arising from the Report of the Kennedy Committee and the Government's Response to these in the light of current knowledge, liasing with the APC and the HO where appropriate;
- identify those recommendations which need to be progressed further;
- identify the actions necessary to do so;
- identify those responsible for carrying out the actions.

In its response to the Kennedy Committee recommendations, the Government said that Ministers would invite the APC to consider the ramifications of xenotransplantation for animal welfare. There is no reference to this in any of the APC reports in the 4 years since the Kennedy Committee report was published.

- We believe the APC should consider this issue in detail (in conjunction with UKXIRA). This does not require an invitation from Ministers. However, we would like to know whether the Government ever did extend this invitation to the APC, and if not, why.

13 Concluding remarks

All of the animal welfare issues in summary sections 12.1 to 12.3 are the responsibility of Imutran because it is their research programme, carried out under

their project licences, which is being reviewed. Our concerns are so serious that we believe that Imutran (and 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.

In so doing, the company should obtain the input of those experienced in primate health, welfare and behaviour to help properly assess the level of primate suffering. They should also be prepared to openly acknowledge the suffering that their research imposes on primates and other animals.

Outside of this specific comment regarding Imutran, we would like to conclude with the following more general remarks. There is 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 and the application of the Three Rs of reduction, refinement and replacement. Of course, it is widely recognised that the cost-benefit assessment that underpins the process by which licences are granted is, by its very nature, subjective. Outside of the inherent difficulty of weighing disparate factors such as costs against benefits, however, there are many different interpretations of what actually counts as a cost in the first place, and 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.

Thus, 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 to reduce suffering, providing channels for progressing new information on the Three Rs (replacement, reduction and refinement) 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. Furthermore, 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.

The RAD has considerable resources and expertise in animal welfare and legislation controlling animal experiments. Our Head of Department is a member of both the APC and UKXIRA. We have been granted access to some of the relevant material and we have read the Chief Inspector's report on the xenotransplantation research conducted on behalf of Imutran, and discussed some of our concerns with HLS. Despite this, 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 Act were actually interpreted in practice.

Xenotransplantation, and the use of animals in experiments, and primates in particular, are serious issues for the public and animal protection organisations. We believe that the questions we have posed throughout this report demand serious 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.

APPENDIX A

Key background information

The RSPCA and animal experiments

The prime objectives of the RSPCA are to promote kindness and prevent or suppress cruelty to animals. With respect to laboratory animals, the RSPCA is opposed to all experiments or procedures that cause pain, suffering or distress. The Society's principal goal is to replace animal experiments with humane alternatives. However, the Society believes that as long as animals continue to be used, every possible effort should be made to prevent suffering at every stage of the animals' lives, i.e. not just during experiments but also as a result of their acquisition, husbandry and care.

The Society adopts a constructive, practical approach to this issue, supporting and promoting the development and adoption of techniques that will result in the replacement of animal experiments, reduction in numbers of animals used and substantial reductions in suffering. The RSPCA is committed to ending the suffering of laboratory primates and believes that the necessity and justification for all primate use should be critically reviewed at a national and international level.

Xenotransplantation

The definition of xenotransplantation used in the Uncaged report (p.5) is *"the transplantation of live organs, tissues or cells between different species".* However, it is important to be aware that xenotransplantation includes cell transplant therapies and extra-corporeal systems as well as whole organ transplantation. Xenotransplantation technology is being developed on an international basis for the treatment of a number of medical conditions and some applications are already undergoing clinical trials in some countries. The wider definition of xenotransplantation means a limited number of standard medical treatments are now considered to come into the category of xenotransplantation.

Animals (Scientific Procedures) Act 1986 (ASPA)

The *ASPA* regulates the use of all vertebrate species of animal plus one invertebrate, (*Octopus vulgaris*), in **"***any experimental or scientific procedure applied to an animal which may have the effect of causing that animal pain, suffering, distress or lasting harm".*

The Act is administered by the Home Office (HO) Inspectorate, which advises the Secretary of State on whether to grant the three kinds of licence required before animals can be used in regulated procedures. These are: (i) a *certificate of designation*, which licenses each procedure, breeding or supplying establishment; (ii) a *project licence*, which has to be obtained for each scientific project; and (iii) a *personal licence*, which permits individuals to carry out procedures under a specific *project licence*.

ASPA also requires that every designated establishment has at least one *Named Veterinary Surgeon (NVS)* and *Named Animal Care and Welfare Officer (NACWO)* - both of whom have statutory responsibilities relating to standards of animal care and welfare within the establishment.

From April 1999, all establishments must have in place an *ethical review process (ERP)* which acts as an adjunct to the HO Inspectorate at a local level. The *ERP* reviews each project before an application is made to the HO and helps to ensure that the *Three Rs* of replacement, reduction and refinement have been implemented.

The *ASPA* sets out an ethical framework for deciding whether or not particular uses of animals are acceptable and can be licensed by the Secretary of State. The broad principles of this framework are that:

1. it must be shown that there is no *alternative* means of achieving the purpose of the work (Section 5.5 of the Act);
2. a '*cost-benefit assessment*' must be carried out for each project proposal, where the welfare 'costs' to each animal are considered against the potential benefits that may accrue from the study (Section 5.4);
3. if the project is considered to be justified and a project licence is to be granted, then *pain, distress, and discomfort* to the animals must be minimised (Section 10.2a).

For more information on the provisions of *ASPA*, see **www.homeoffice.gov.uk/animact/aspileaf.htm**

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21 June 2002