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PART I

SETTING THE SCENE: XENOTRANSPLANTATION, ETHICS AND THE REGULATION OF PRIMATE VIVISECTION

CHAPTER 1

Introduction

1.1 Controversial research

Xenotransplantation is the transplantation of live organs, tissues or cells between different species. Such transplants are also referred to as **xenografts**.

This report 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. The material includes 39 draft reports describing xenotransplantation experiments on higher primates commissioned by the UK biotechnology company **Imutran Ltd** and conducted by **Huntingdon Life Sciences** at their Cambridgeshire laboratories. Other documents include correspondence, meeting minutes, feasibility studies and internal reports concerning many aspects of the conduct of and plans for xenotransplantation research.

The experiments have predominantly involved the transplantation of hearts and kidneys from **genetically-engineered pigs** into two species of higher primates, **baboons** and **cynomolgus monkeys**. Following transplantation, the primates have been administered experimental cocktails of drugs in an effort to suppress their immune systems and thus prevent rejection of the pig organs. Through conducting this research, **Imutran**, the Cambridge-based biotechnology subsidiary of the multinational drug firm **Novartis**, hope to develop a package of treatments consisting of transgenic pig organs and accompanying immunosuppressive therapies to sell through health care providers to patients with malfunctioning organs.

Quite apart from the revelations of the acquired documents, xenotransplantation research has been controversial because:

- If xenotransplantation ever proved successful, the use of genetically-modified pigs as sources of organs would signify a novel form of suffering, exploitation and death deliberately inflicted by human society on nonhuman animals.
- The extensive use of higher primates in procedures that have caused very high levels of suffering.
- Complex species differences between non-human primates and human beings that render results gained by experiments on the former unreliable as a guide to the human situation.
- The contracting of this research programme to **Huntingdon Life Sciences**, a commercial research company whose track record includes breaches of animal welfare and Good Laboratory Practice regulations.

- The profoundly difficult problems faced in trying to overcome the rejection of pig organs by the human immune system.
- Serious doubts exist about the physiological and biochemical compatibility of pig organs with the human body.
- The potential of xenotransplantation to introduce novel infectious organisms such as retroviruses into the human population, thereby causing new pandemics with echoes of HIV/AIDS.
- The existence of alternative methods of tackling the health problems of organ failure such as preventative health measures, increasing the pool of human donors, mechanical devices or growing new organs from human cells.
- The distributive justice of xenotransplantation: whether it represents the most efficient and most equitable use of scarce health resources.¹
- The commercial motivation behind the research, which adds up to an attempt to dominate a market that is predicted to be worth \$11 billion by 2010.²

Another controversial element of Imutran's xenotransplantation research centres on the housing conditions of transgenic pigs. The acquired information does not focus on the procedures affecting pigs, apart from descriptions in the study reports of their dismemberment and killing in order to derive organs for experimental transplantation into the primates. Nonetheless, it is important to note the impact that xenotransplantation is having on these animals. In order to minimise the risk of the transgenic pigs acquiring any pathogens which could then be passed on to future recipients of xenografts, the pigs are kept in what is known as Qualified Pathogen Free (QPF) conditions. Pigs are highly intelligent, complex and sociable animals. When given the opportunity under natural conditions, they will spend some 75% of their daylight hours in rooting, foraging and exploratory activities. QPF conditions require a relatively barren, indoor environment that will deprive pigs of the chance to satisfy adequately their desire to explore and forage, leading to behaviours indicative of psychological suffering such as stereotypical behaviour and aggression. Indeed, an undercover investigation has discovered fighting among Imutran's pigs.³ In a letter to Uncaged Campaigns, the RSPCA has stated:

The RSPCA has always expressed extremely serious concern at the welfare implications of keeping pigs in SPF/QPF conditions. We believe that this seriously curtails one of the Five Freedoms widely recognised as important for farm animals.

Additionally, the RSPCA responded to the Kennedy Report⁴ by submitting:

¹ See, for example, Dr Richard Nicholson. If pigs could fly. *Nursing Times*, 3 February 1997: 20.

² Stephen D. Moore. Novartis Picks up Pace in Xenotransplant Race. *Wall Street Journal (Europe)*, 10 October 1997: 4.

³ *Genetically Engineered Pigs at Harlan UK: A Supplementary Report from the BUAV July 1999*.

⁴ The 'Kennedy Report' refers to *Animal Tissue Into Humans*, the report by the Government-appointed Advisory Group on the Ethics of Xenotransplantation which was chaired by Professor Ian Kennedy. The report was published by the Government in January 1997.

The RSPCA is seriously concerned that the recommendation relating to the maintenance of animals in biosecure conditions will result in environmentally sterile and barren accommodation.

Requirements for the surgical derivation of piglets and their early weaning also lead to distress for both mother sow and piglet. Source piglets will be weaned as young as 5 to 7 days, an acknowledged breach of the Welfare of Livestock Regulations 1994. The Home Office, however, condones this to facilitate the development of xenotransplantation.⁵

1.2 New information

The hitherto secret information presented via this report confirms and intensifies these fears, particularly in terms of the intense suffering of primates and the implausibility of viable xenotransplantation. Additionally, new concerns are raised about the standards of laboratory practice during the studies and the extent to which the Home Office has fulfilled its duty to enforce regulations pertaining to animal experiments and limits on the suffering of animals.

- **Animal suffering.** The true extent of the suffering inflicted on higher primates is now revealed - from capture and/or captive breeding in the tropics... on through highly stressful and sometimes lethal long-distance transportation in close confinement⁶ ...ending with the extreme torment of the xenotransplantation experiments themselves.⁷ The following clinical observations, recorded in the acquired study reports, are a snapshot of the misery endured by hundreds of primates at the hands of HLS and Imutran. The first notes are for the last two days in the life of baboon W205m, who died in a study involving the transplantation of transgenic pig hearts into the necks of wild-caught baboons.⁸

20	am	Quiet but alert. Scab on operation site appears clean and dry. Keeps holding area where transplanted heart is.
	pm	Quiet and huddled. Little movement and unsteady when moving. Showing signs of discomfort.
21	am	Quiet and huddled. Scab on operation site appears dry. Reluctant to move. Marked firm swelling around implant. Animal showing obvious discomfort. Fluid swelling developing in sub-mandibular region.
	pm	Sero-sanguinous fluid drained but no purulent material. Transplanted heart beat barely palpable. Swelling so large animal sacrificed for humane reasons.

⁵ See paragraphs 1.1–1.13, 2.3, 4.3, 4.5.4 in draft Home Office Code of Practice for the Housing and Care of Pigs Intended for use as Xenotransplant Source Animals at <http://www.homeoffice.gov.uk/ccpd/aps.htm>

⁶ See Chapters 3 & 5 for a discussion of these issues.

⁷ For the raw data detailing the suffering of the primates during the experiments, see the clinical signs appendices with each study report.

⁸ See section 4.1. Also see clinical signs for study ITN6-972924.

And these clinical signs relate to a cynomolgus monkey T397m, into whose abdomen a transgenic pig kidney was transplanted.⁹

21 am	Quiet, huddled on perch, reluctant to move. No reaction to external stimuli, vacant appearance. Clear nasal discharge. Liquid faeces in cage.
pm	Quiet, huddled on perch, reluctant to move. No reaction to external stimuli, vacant appearance. Clear nasal discharge. Liquid faeces in cage. Collapsed following administration of parenteral dosing. Some recovery, very quiet, sitting holding perch. Little interest in surroundings.
22 am	Quiet and huddled. Reluctant to move. Constant grinding of teeth. Liquid faeces.

Additionally, over a quarter of the animals died on the operating table or within a few days because of technical failures in the surgical procedures.¹⁰

- **Lack of progress.** In 1995, Imutran predicted that the first human trials of their transgenic pig organs would take place the following year.¹¹ But despite an intensive research effort that has sacrificed hundreds of higher primates and thousands of pigs, the goal of achieving viable xenotransplantation remains as remote as ever. The development of the particular line of transgenic organs that Imutran have been testing for five years – known as hDAF – appears to be in crisis, with Novartis setting an 18 month time limit (from April 2000) for achieving a quantum leap in survival times.¹²

In order to try and attain this progress, this spring (2000) Imutran appear to have abandoned primate research in the UK and, instead, are coordinating the activities of a group of external collaborators [REDACTED]. One of the US collaborations (the [REDACTED]) was set up in 1999 “following the selection of first potential sites for clinical trials in the US, and includes the [REDACTED]”¹³

- **Public health risk.** The possibility of risks to public health are raised by the involvement of human transplant surgeons [REDACTED] in experiments on wild-caught baboons who appear to have been carrying the potentially lethal Simian Herpes B virus.¹⁴

⁹ See Section 6.5 and clinical signs for study ITN4-973128.

¹⁰ See Chapters 4 and 6.

¹¹ Nuala Moran, "Pig-to-human heart transplant slated to begin in 1996", *Nature Medicine*, 1:10, October 1995: 987.

¹² See file [REDACTED]

¹³ See file [REDACTED]

¹⁴ See section 3.3 and document WCB22.1.

- **Errors and omissions in the conduct of the studies.** Another feature of the evidence contained in the acquired documents relates to the manner in which the studies were performed. On several occasions Imutran expressed dissatisfaction with the level of service provided by Huntingdon Life Sciences (HLS)¹⁵, claiming in one instance that some studies exhibited “a fundamental shortfall in GLP compliance.”¹⁶ Throughout the research programme, we estimate that 520 separate data recording errors and failures occurred.¹⁷ The illegal re-use of a group of monkeys took place at HLS.¹⁸ The most heated criticism arose from two incidents that took place within a month of each other in winter 98/99. Firstly, a monkey was accidentally given a quadruple overdose of an immunosuppressant drug – she died the next day. Secondly, a vital blood sample was taken at completely the wrong time, thereby hindering attempts by Imutran to calculate the optimum dose of immunosuppressant drugs.¹⁹

Imutran themselves do not appear to be blameless. Seven baboons appear to have been transplanted without a crucial antibody reading being taken before the surgeries.²⁰ On another occasion, a monkey died four days after being vivisected because of a swab left inside him that caused his spleen to go septic.²¹ In another accident, a piglet kidney due to be transplanted into a monkey was frozen and thus rendered useless, leading to the monkey being killed while under anaesthetic in preparation for the transplant.²² Later on, several discrepancies in the pathology reports for a group of primates leads Imutran’s ██████████ to comment that the company’s attainment of international quality management standards (ISO9000) was in jeopardy.²³

The failures and omissions may have compromised animal welfare in certain instances, and generally they had the potential to undermine the reliability and usefulness of the data generated by the experiments. The latest documents reveal that Imutran have “severe problems”²⁴ with the state of the data from these studies. Given the intense suffering inflicted on primates and the costs in terms of the lives of the primates and the pigs, the very least one should expect from this research project is that the studies produce optimum quantity and quality of information.

- **Home Office failures.** The documents reveal the Home Office’s failure to enforce the regulatory framework for animal research. In the first instance, the severe and prolonged suffering of many animals potentially breaks absolute

¹⁵ See chapter 7.

¹⁶ See section 7.3 and document HLSAPP2.

¹⁷ See section 7.6.

¹⁸ See section 7.5 and document HLSAPP5A.

¹⁹ See section 7.8 and HLSAPP7C.1, HLSAPP7D.1 & HLSAPP7D.2 .

²⁰ See end of section 4.3, and WCB22.1.

²¹ See section 6.5, subsection ‘Study IAN020’ and CY22.2, HLSAPP7A.3 & HLSAPP7B.2.

²² See HLSAPP7B.2 and clinical signs for IAN020 (p.135).

²³ See HLSAPP7B.1.

²⁴ See HLSAPP8B.1.

limits enshrined in British and European legislation that are supposed to outlaw such extreme distress. Secondly, the Home Office must apply a cost-benefit assessment to decide whether to permit a programme of animal experimentation. This formula is a central feature of the legislation governing animal experimentation in the UK.²⁵ However, the costs inflicted on animals in the course of xenotransplantation research appear to far outweigh any reasonable assessment of the benefits likely to accrue.

The Home Office decided to re-issue Huntingdon Life Sciences (HLS) with a new Certificate of Designation in 1997. In re-issuing the Certificate, the Home Office accepted that HLS had satisfied 16 conditions which were designed to prevent incidents of malpractice at the company, some of which were exposed by an undercover investigation broadcast on Channel Four in March 1997. This new evidence casts doubt on the basis of the Home Office's decision.²⁶ For example, just one month after the Home Office had given a new Certificate to HLS, a group of monkeys were illegally re-used in experiments at the establishment. This breach of the law should have been prevented by the implementation of the improvements that formed the 16 conditions laid down by the Home Office that HLS should have fulfilled to retain a Certificate of Designation - but the Home Office did not revoke HLS' Certificate in the light of these illegal procedures.²⁷ Errors and omissions in the conduct of the studies also took place during the period when HLS were said to be in the process of meeting the 16 conditions, and directly afterwards (e.g. the illegal re-use incident).

Other incidents of regulatory inaction included the response to the deaths of three cynomolgus monkeys during transit from the Philippines to HLS for xenotransplantation research: the crates that held the monkeys had broken regulations on size and ventilation.²⁸ In one confirmed instance, the journey time for an importation of wild-caught baboons was considerably longer than the estimate submitted on Imutran's application form. The Home Office appears to have asked for some assurance from Imutran that the same baboons, who arrived in May 1999, would be used relatively quickly in recognition of the suffering imposed on them by the laboratory environment.²⁹ However, the animals languished at HLS for at least seven months. Additionally, other wild-caught baboons imported previously had been incarcerated for up to two years in conditions that appear to have been inferior to those experienced by the May 1999 contingent.

The following sentence to emerge from the minutes of a meeting at Imutran is revealing: "██████████ [the local Home Office Inspector for Imutran] has on several occasions expressed his view that the new License will be approved before the existing license is revoked and that Thursday [i.e. a meeting of the Animal Procedures Committee (APC) – the Government's advisory committee

²⁵ The Animals (Scientific Procedures) Act 1986, section 5(4).

²⁶ See Sections 7.5 & 7.8.

²⁷ See section 7.5 and HLSAPP5A.

²⁸ See section 5.2 and CY5.

²⁹ See WCB26

- to discuss the licence application] will be merely a ‘rubber stamping’ exercise.”³⁰

In the context of the relationship between the Home Office and Imutran, another significant comment came from Imutran’s [REDACTED] [REDACTED], as he outlined the points to emerge from a company meeting that took place towards the beginning of the primate vivisection programme in spring 1995:

“[REDACTED] – [REDACTED] of Imutran [REDACTED] [REDACTED] agreed to talk to [REDACTED] [REDACTED] an Inspector] at the Home Office re technical failures, life-supporting heart in baboon and to generally chew the cud and ensure smooth and rapid passage of forthcoming 19b. application. Important that [REDACTED] understands the issues (technical difficulty, imminence, etc.) and will give us upward support of the application for orthotopic work. We have to work to make him look like a jolly good bureaucrat and yet achieve our goals as well!”³¹

1.3 Public interest

The justification for publishing these confidential documents arises from the right of the public to know the full facts of this hugely significant research programme.

- Transplant patients have been led to believe that xenotransplantation is likely to provide a solution to the lengthy waiting lists for organ transplants. These patients and their families have a deep interest in knowing the true state of progress with this technology, and whether it really does offer a realistic and attractive option.
- Public funds (e.g. from the Medical Research Council [REDACTED]) have been used to support research into xenotransplantation and to oversee its regulation by the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA).
- Ultimately, decisions about whether to permit clinical trials of xenotransplantation procedures will be taken by the Government. It is important that the public, whose interests the Government must represent, has complete knowledge of the background of this technology in order to make as informed a decision as possible on such a momentous issue.

³⁰ See CY24.2.

³¹ See I3.1.

- There is a clear public interest in establishing the facts about the possible threat posed to public health by the use in research of wild-caught baboons and other primates who may be carrying the dangerous Simian Herpes B Virus and other potential pathogens.
- The question of the correct and effective execution of the rule of law by the Home Office is an issue of public interest. This report raises doubts about the Home Office's operation of the Animals (Scientific Procedures) Act 1986 and the adherence to European law forbidding the infliction of severe pain and distress on animals.
- Question marks over the Home Office's conduct are also raised by the acquired documents insofar as they throw into doubt the accuracy of the pronouncement of a Home Office Minister in October 1997 that HLS had satisfied 16 conditions set by the department in the wake of a damning undercover investigation.
- The adherence of studies intended for regulatory submission to Good Laboratory Practice is another important issue of public interest to be highlighted by this report.
- The victims of this research have been the higher primates and the pigs. The "public interest" is not the only legitimate interest in this affair, a point confirmed – ironically – by the stipulation in the Animals (Scientific Procedures) Act 1986 that the interests of animals should be taken into account in determining whether to licence vivisection procedures. A true democracy reflects the principle that those affected by decisions must have an input – where necessary, voiced by an advocate - into the decision-making process. Thus the interests of non-human animals have a vital role to play in democratic government, particularly when policies affecting their interests are being formulated and executed.
- Lastly, there is a clear public interest in the ethical issue of how our society treats nonhuman 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 ourselves and our society. A significant proportion of the public do take a deep interest in the treatment of animals.

Before we briefly outline the structure of this report, it will be useful to provide a rough sketch of the development of xenotransplantation and, in particular, Imutran's research programme.

1.4 Development of xenotransplantation

Sporadic attempts have been made to transplant animal organs into human beings since the early 1900s. All of these efforts have failed, with the longest (by some way) survival period attained being nine months in the case of a school teacher who received a chimpanzee kidney heterotopically (i.e. the xenograft was transplanted alongside his own kidney) in the United States in 1963.³² Three principle obstacles have lead to the failure of xenografts:

1. biochemical and physiological incompatibilities between nonhuman organs and the human body;
2. rejection of the nonhuman organ by the human immune system;
3. infection, usually as a result of the high doses of immunosuppressive drugs administered in an effort to temper the rejection process.³³

The main organs that are allotransplanted are kidneys, livers, hearts and lungs. Initial developments in the field of allotransplantation (human-to-human transplantation) in the 1960s were a major spur to experimental xenotransplantation procedures. But the advances gained in the area of immunosuppression and improved surgical techniques with allotransplants failed to translate to the case of xenotransplantation because of the precipitous biological barriers faced by the latter. As allotransplantation has developed, the demand for human organs for transplantation has steadily increased as more patients have been able to potentially benefit from the operation. However, the demand for organs now outstrips the current supply in many countries.

The development of genetic modification techniques in the 1990s, coupled with the gap in the market for organs, has encouraged biotechnology scientists and companies to research xenotransplantation once more. Specifically, it is hoped that by genetically altering pig organs, it might be possible to overcome the particularly virulent immune response suffered by xenografts. Whether this is a reasonable proposition is debatable, but, nevertheless, it is this research that Imutran has spearheaded.

Imutran was founded in 1984 [REDACTED]

[REDACTED] By gaining understanding of an element of the human immune system known as **complement**, and developing techniques for genetically manipulating animal organs in an effort to regulate human complement activity, Imutran are intent on realising their vision of successful xenotransplantation.³⁴ In 1996, Imutran were bought by the Swiss pharmaceutical corporation Sandoz who, at the time, produced the immunosuppressive drug [REDACTED] which dominates the transplantation market. Later in 1996, Sandoz merged with another drug company, Ciba Geigy, to form Novartis. [REDACTED] is one of Novartis's best-selling drugs. However, its sales are limited by the number of transplants that take place. Developing xenotransplantation was a move designed to overcome these limitations, thereby maximising sales of

³² Kennedy Report: 9.

³³ Kennedy Report: 9-10.

³⁴ Imutran. Imutran (promotional booklet), Cambridge (undated).

██████. Novartis has pledged to invest up to \$1 billion in the development of xenotransplantation.³⁵

1.5 Immune rejection of xenotransplants

The body's immune system attempts to destroy, or to "reject" as it is often termed, entities which it recognises as "foreign". The immune response to a transplanted organ is triggered when components of the immune system identify molecules called *antigens* as being different to the antigens borne by the body's own tissues. Antigens are found on the surfaces of the organ, particularly the inner lining, or *endothelium*, of blood vessels in the organ. Rejection of human organs is a familiar phenomenon in allotransplantation: the immune response can be tempered by matching the tissue of the donor and the recipient as closely as possible (so that they share a maximum number of antigens). However, drugs which suppress the immune system still have to be used in order to subdue the immune response to the transplanted organ.

The immune response increases in severity in proportion with the discordance between source tissue and recipient. Thus, rejection in the case of xenotransplantation is both considerably more aggressive than with allotransplantation, as well as being qualitatively different.³⁶ Xenografts themselves can be divided into two groups, depending on the evolutionary distance between source animal and recipient: *discordant* and *concordant*.

The distant evolutionary relationship between pigs and humans leads to an extremely strong immune response to pig-to-human transplants – a response that cannot be controlled with immunosuppressant drugs. This is a discordant xenograft. Discordant xenografts give rise to a particularly aggressive and swift form of rejection not usually seen in concordant xenografts and allografts called *hyperacute* rejection. Three further types of rejection have also been identified through observation of allotransplantation operations: acute vascular, acute cellular and chronic rejection.³⁷ However, in the case of discordant xenotransplantation, hyperacute rejection is the first barrier to be overcome before attention can be focussed on these and hitherto undiscovered subsequent immune responses to the transplanted organ.

Despite the additional immunological hurdles to be overcome and growing public opposition, Imutran's research has focussed on developing pig organs for xenotransplantation. The main reasons why primate xenografts have fallen out of favour appear to be: deeper public disquiet over the use of primates as source animals compared to pigs; differences in body size and life expectancy between human and nonhuman primates; a perceived higher risk of transferring infectious organisms from nonhuman primates to humans; and greater difficulties in producing sufficient numbers of organs. On the other hand, pig organs are said to be comparable in size

³⁵ Anon. Affairs of the heart. *The Economist*, 4.4.98: 106. Stephen D. Moore. Novartis Picks up Pace in Xenotransplant Race. *Wall Street Journal (Europe)*, 10 October 1997: 4.

³⁶ Nuffield Council on Bioethics. *Animal-to-Human Transplants: the ethics of xenotransplantation*. London: Nuffield Council on Bioethics, 1996: 25 [hereafter referred to as 'Nuffield']. Kennedy Report: 9.

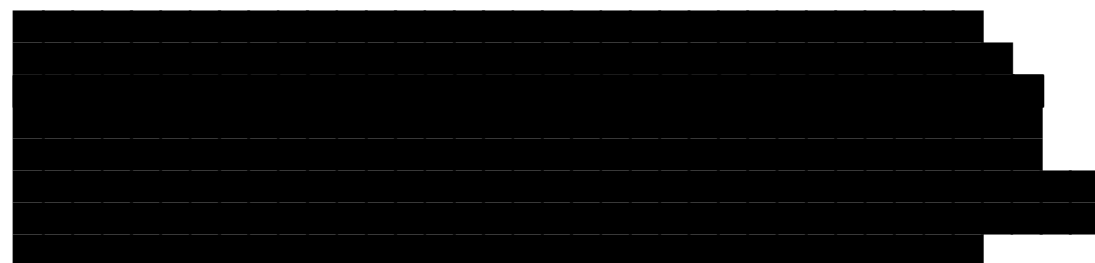
³⁷ Kennedy Report: 20.

with humans; the exploitation of pigs in agriculture, it is thought, will stifle protests regarding their exploitation for the production of organs; and pigs breed relatively rapidly and prolifically compared to primates, thereby potentially producing more organs.³⁸

Hyperacute rejection occurs when antibodies that naturally exist in human blood - xenoreactive natural antibodies (XNAs) - bind to particular antigens (Gal-epitope molecules) on the cells that line the inside of the vessels within the transplanted pig organ.³⁹ An important consequence of the binding of antibodies to antigens is the activating of a complement reaction against the "foreign" organ. Complement is a group of proteins in the blood. A complex chain reaction among these proteins results in some of the complement causing inflammation and damage of the organ's cells. White blood cells are also activated by the complement proteins and join the attack.⁴⁰ This hyperacute reaction is so swift that the xenograft fails in minutes, or sometimes even within seconds.⁴¹

Normally, complement is prevented from attacking the cells of the body by proteins (Regulators of Complement Activity - RCAs) which exist on the surface of cells. However, these RCAs are species-specific, with particularly wide differences between distantly-related species [e.g. pigs and humans]. In other words, usually, pig cells carry RCAs which regulate pig complement activity but will fail to prevent human complement proteins from attacking the cells in the event of xenotransplantation, leading to hyperacute rejection.⁴²

The strategy devised by Imutran to try to overcome hyperacute rejection has involved the identification of the human genes that contain the code for the production of human RCAs, and their subsequent introduction into pigs in the hope that the cells of the pig express the human RCAs. An important human RCA has been identified, known as DAF (Decay Accelerating Factor). Through molecular biological techniques, the human DAF (hDAF) gene has been introduced into pigs, making them *transgenic*. As with all genetic engineering, only a small proportion of these pigs actually express the relevant gene and produce the hDAF in useful quantities. Through selective breeding, however, herds of "suitable" transgenic pigs have been built up. Imutran have developed a large herd of transgenic pigs containing the hDAF.⁴³



³⁸ Kennedy Report: 16-17.

³⁹ Kennedy Report: 21.

⁴⁰ Nuffield: 32.

⁴¹ Kennedy Report: 20,21.

⁴² Kennedy Report: 21.

⁴³ "The generation of transgenic pigs as potential organ donors for humans." *Nature Medicine* 1995, 1: 964-6. Cited in Nuffield: 33. Imutran. *Imutran* (promotional booklet), Cambridge (undated): 5.

[REDACTED]

In 1995, Imutran believed that the insertion of the hDAF gene had circumvented hyperacute rejection in the nonhuman primate recipients of transgenic pig organs. However, the mechanisms behind hyperacute rejection are still far from fully understood, and some organs have been hyperacutely rejected despite the expression of hDAF on the graft endothelium. (Indeed, in a recent confidential document dated early 2000, Imutran admit that the prevention of HAR “is not complete.”⁴⁴) Nonetheless, having assumed that they had overcome the hyperacute rejection (HAR) of pig organs in nonhuman primates in 1994/1995, Imutran appeared confident that the remaining hurdles to successful xenotransplantation would be straightforward. According to a report in *Nature* in September 1995, Imutran reportedly:

“...told a press conference in London that 10 monkeys, each of which had been given a heart from one of the company’s herd of transgenic pigs, had already survived for an average of 40 days, and that two were still alive after 60 days.”

Following this announcement, Imutran claimed that its xenotransplantation technology was “now ready to be tested in humans”: clinical trials were predicted to take place the following year [REDACTED]

[REDACTED]⁴⁵

The *Nature* article does report claims from more circumspect researchers who argued that clinical trials would be premature:

“They claim in particular that more needs to be understood about other longer-term mechanisms in addition to HAR which can lead to eventual transplant rejection.”

However, Imutran’s [REDACTED] dismissed these concerns:

“A lot of people have said that [tackling the problem of HAR] was only the first of many hurdles,” he says. “But as far as we can see, the other hurdles have not raised their head in the timeframe of our experiments.”

But the sceptics appear vindicated; Imutran’s grasp of the biological complexities intrinsic to the xenotransplantation of porcine organs is less than complete. The main obstacle for the past five years has been the subsequent rejection processes. As a briefing in the journal *Nature* put it:

“In the cold dawn of the 4th International Conference on Xenotransplantation last autumn [1997] in Nantes, France, it was clear that optimism resulting from

⁴⁴ See document [REDACTED]

⁴⁵ David Dickson. Pig heart transplant ‘breakthrough’ stirs debate over timing of trials. *Nature*. Vol 377, 21 September 1995: 185.

progress in overcoming HAR had given way to the realization that many factors playing a role in organ rejection are still far from understood."⁴⁶

In order to understand and try to control these subsequent rejection processes, Imutran have vivisected at least 473 higher primates and thousands of pigs in the UK, and an unknown number of animals through collaborations with researchers in the US, Canada, Spain, Italy and the Netherlands. Despite the sacrifice of these animals, research into xenotransplantation is in deep crisis. Because of the lack of progress due to the profoundly inscrutable immunological obstacles to xenotransplantation, and the persistent danger of transferring viruses from pigs to humans, Novartis set an 18-month time limit in April 2000 to evaluate, once-and-for-all it seems, whether xenotransplantation with the hDAF pigs is feasible. Through the coordination of a network of international collaborators and the vivisection of a further 150 baboons and cynomolgus monkeys, Imutran have been charged by Novartis with achieving the effective management of rejection and substantial increases in survival times towards criteria laid down by the United States Government's regulatory body, the Food and Drug Administration (FDA), as a prerequisite for clinical trials.⁴⁷ However, the targets set by the FDA would require a quantum leap in the progress of xenotransplantation – far greater than that achieved in the past five years.

But even if the hDAF pig is abandoned, this may not signal the end of xenotransplantation research. There are alternative human RCAs to hDAF, and the confidential documents reveal that Imutran has already been experimenting by inserting the genes that code for the expression of alternative human RCAs into pigs.⁴⁸ The documents demonstrate that Imutran have considered continuing lethal experimentation on pigs and higher primates in the hope that they discover the magic formula for turning transgenic pig organs into a multi-billion dollar product – biotechnological alchemy.

1.6 The structure of the report

Having created the hDAF transgenic pig, Imutran have sought to investigate the transplant potential of organs from such animals by testing them in the 'cousins' of human beings: nonhuman higher primates - specifically baboons and cynomolgus monkeys. It is this research project, as revealed by the extensive cache of leaked documents and study reports, which is the major focus of this report.

Until this point in time, available information concerning this controversial research project has been minimal. Occasionally, Imutran have published scientific papers which have provided glimpses of their experiments. However, this report and the documentation upon which it is based provide the public with an unprecedented and extensive insight into the reality of animal experimentation in modern Britain.

⁴⁶ Nature 22 January 1998, Volume 391 No. 6665.

⁴⁷ See document [REDACTED]

⁴⁸ See document [REDACTED]

The report is split into five parts. Part I sets the scene by describing the context of this programme of vivisection. This chapter has provided some background information about the multi-faceted controversial nature of xenotransplantation, an overview of the most salient points to emerge from the leaked documents, and the rationale behind the development of transgenic pigs as a potential source of xenografts. Chapter 2 presents the victims of this research, higher primates, to describe the suffering they endure. We also explain to the reader the legal framework, centred around the Animals (Scientific Procedures) Act 1986, which the Home Office must implement to regulate animal experimentation.

Parts II and III tell the story of the baboons and cynomolgus monkeys, from capture in the wild, through transportation half way across the world, to their experience in the experiments themselves at Huntingdon Life Sciences. Part IV scrutinises the role of Huntingdon Life Sciences. Part V draws together the various themes to emerge from the leaked documents, to analyse whether this research programme has been correctly conducted and regulated. Finally, we offer our conclusions and recommendations.

CHAPTER 2

Primates and the regulation of animal experiments

The hitherto unpublished information, comprising 39 study reports together with other company documents, records the history of xenotransplantation experiments commissioned by Novartis subsidiary Imutran Ltd at Huntingdon Life Sciences (HLS) from 1996 until spring of this year (2000). It provides a unique insight into one of the most controversial and significant programmes of animal experimentation ever to take place in the United Kingdom.

In addition to some 10,000 pigs, two species of higher primates – baboons (*Papio anubis*) and cynomolgus monkeys (*Macaca fascicularis*, also commonly known as ‘crab-eating macaques’) - have been used extensively: 49 wild-caught baboons have been sacrificed for this research project, together with 424 cynomolgus monkeys. Since the end of experiments on Great Apes in the UK, these are the closest relatives of humans to have been subjected to vivisection procedures for several years.

For the most part these primates have been used as test beds for transplants of transgenic pig hearts and kidneys and accompanying immunosuppressive regimens. Imutran’s aim has been to achieve success in these “models” in terms of sufficiently extended survival times in order to move to clinical trials.

This chapter sets the scene for the remaining Parts II, III and IV of this report by describing the regulatory framework within which animal experimentation is licensed in the UK. The reader, as a consequence, will be able to assess

1. whether this programme should ever have been permitted in the UK; and
2. the adequacy of the Government’s on-going regulation of the project.

The law requires that the regulators take account of the suffering to which the animals are subjected during the experiments. This chapter, therefore, commences with a brief description of the complex lives of non-human primates in order to help the reader to appreciate the deeply traumatic and painful experiences these animals have endured during the course of their capture, captivity, transportation and, finally, the lethal transplantation procedures. The most important question that this report can raise through the publication of the records of the demise of these primates is: Can the infliction of such suffering and death ever be justified?

2.1 Non-human primates: affinities with humans

The two major British bioethical reports into xenotransplantation^{49,50}, both discuss the moral standing of primates and the serious ethical questions raised by their use. One

⁴⁹ Animal-to-Human Transplants: the ethics of xenotransplantation. Nuffield Council on Bioethics. March 1996. Henceforth referred to as the “**Nuffield Report**.”

of the main sources of moral concern over experimentation on species of higher primates arises as a result of their relatedness to human beings. The Nuffield Report states:

“There is evidence that some animals, notably the higher primates, have much in common with human beings, including self-awareness, complex social relationships and many of the other characteristics that have often been supposed to make human beings unique.” (p.40 - * Parker S and Gibson K eds. (1990) “Language” and intelligence in monkeys and apes. Cambridge: Cambridge University Press.)

“The close evolutionary relationship of higher primates with human beings suggests that they will share the capacity for self-awareness to the highest degree, and there is good scientific evidence that this is the case.” (p.47)

“Serious ethical concerns are raised by the possible use of primates for xenotransplantation. The sophisticated capacities of primates suggest that any harm suffered by them should be given great weight.” (p.50)

Similarly, the Kennedy Report refers to the close affinities of primates with humans, and their undeniable mental capacities and self-awareness that, in turn, increase their capacity for suffering. (p.65)

The following extract comes from a collection of essays discussing the use of animals and describes the lives that baboons enjoy when free in the wild, and cautiously hints at the corresponding suffering they endure in captivity:

“In her book *Almost Human*, primatologist Shirley Strum describes the rich and complex lives of baboons living in troops on the African savannah.* Individual baboons have a variety of intricate and demanding social relationships with other members of their troops. They engage in a multitude of activities, including communication, reciprocal grooming, play, and infant care, which is performed by both sexes. Although life in captivity offers protection from certain natural and human threats encountered by freely ranging baboons, it also provides baboons with many fewer opportunities to exercise their normal mental, social, and physical capacities. It is possible that captive baboons experience frustration and other forms of subjective deprivation from their relatively sterile environments.”⁵¹

Social awareness and accompanying deceptive behaviour are taken by experts in animal consciousness as some of the defining aspects of a highly self-aware and complex mind, not least because they seems to require a sense of the other mind as

⁵⁰ Animal Tissue into Humans. Advisory Group on the Ethics of Xenotransplantation (Department of Health). August 1996. Henceforth referred to as the “**Kennedy Report**,” after the chairperson of the Group, Professor Ian Kennedy, who has since become chairperson of the Nuffield Council on Bioethics.

⁵¹ The Human Use of Animals: case studies in ethical choice. F Barbara Orlans et al. Oxford University Press, 1998: 39. * Almost Human: a journey into the world of baboons. Shirley Strum. (New York: Random House, 1987).

well as one's own. George Page describes the following incidents in his book *The Singing Gorilla: understanding animal intelligence*:⁵²

“Marc Hauser reports that the macaques he observes on the Puerto Rican island of Cayo de Santiago (‘Monkey Island’) routinely assess the social situation before calling out about a new food source. Who’s around? Friend or foe? Kin or non-kin? These are critical concerns, because if the monkey lies, in effect, by not reporting the food with foes and non-kin around, they will rough him up. What’s most fascinating to Hauser is the behaviour of the ‘peripheral male’ who isn’t a member of any group. This male almost never makes a food announcement and, even when caught, is never beaten up. This suggests that the rules of engagement, so to speak, are specific to the one social group.” (pp.206-207)

“An episode of deception which ‘made the rounds’ – and therefore the literature – among ethologists was the behaviour of the female baboon who sneaked away from the alpha male in her troop and mated with a young male behind a rock, unseen by the alpha. Moreover, she peeked out from behind the rock, apparently to make certain that the main male remained oblivious to her infidelity. Similar behaviour has been observed among the macaques on Cayo de Santiago. There have also been many reports of primates engaging in ‘acoustic hiding’, as it’s called – repressing the usual sounds of sexual behaviour if this behaviour might run afoul of the established order.” (pp.207-208)

Grief is referred to as a higher-order emotion, and its presence in the animal kingdom reinforces the realisation of psychological continuities between humans and other animals:

“One of our most moving Nature films ever was about a group of Japanese macaques which had been filmed over several years by Japanese researchers. Our star was Mozu, and we called the film Mozu the Snow Monkey. During the filming, one of Mozu’s relatives gave birth to a stillborn baby. The mother would not leave her dead baby – in fact she would not let go of it. She carried its little body everywhere.

At night she would climb up into a particular tree, hold the dead baby in her arms and scream. It was the most blood-curdling scream I have ever heard. She did this for three days and three nights. On the fourth day, she put the body of her baby on the jungle floor and disappeared into the jungle herself.” (p.169)

The primates that have suffered and died at the hands of HLS and Imutran were not just statistics or abstract numbers on a data sheet. They were living, feeling individuals. To fully absorb and appreciate the significance of the clinical signs and the other information describing the fate of these animals, the reader must make him

⁵² *The Singing Gorilla: understanding animal intelligence*. George Page. Headline, 2000. Back cover: “George Page has been producing science television programmes for many years. He created the acclaimed natural history series *Nature* in the United States and was Executive Editor of the BBC’s *Animal Minds* in 1998.”

or herself aware of the true context of the situation. In particular, if one bears in mind the emotional similarities of higher primates with humans, then one can easily empathise with the experiences of the hundreds of monkeys and baboons to have been vivisected as part of this research programme – and be conscious of its true horror.

2.2 The “regulation” of animal experiments

The law that regulates animal experimentation in the UK is the **Animals (Scientific Procedures) Act 1986** (A(SP)A). To conduct experiments on animals, an individual must apply for and receive a **personal licence** from the Home Office, the government department that administers the Act. A personal licence holder may then submit to the same department what is known as a “**project licence application**” for a particular programme of animal research. Project licences may be complex and large, and one project licence holder, who has overall responsibility for the procedures carried out on animals within the project, may have several personal licence holders working under him/her in the course of the project. Establishments that host programmes of animal experimentation must have gained a **Certificate of Designation**. There are conditions attached to all three approvals, the breaching of which is supposed to jeopardise the possession of the pertinent licence, and also result in a possible criminal conviction. Additional regulatory processes must be completed in certain cases, such as the acquisition of primates for research from overseas suppliers and the importation and use of wild-caught primates. The use of primates from overseas suppliers – some of them taken from the wild - are central aspects of the licensing of xenotransplantation research and will be discussed below.

The licence applications to conduct the research in question were submitted to the Home Office by [REDACTED], Imutran’s [REDACTED]. The surgeons conducting the xenotransplantation surgeries on animals should be personal licence holders. Huntingdon Life Sciences (HLS), the venue for the experiments, must have a Certificate of Designation.

Project licence applications are a key stage in the licensing process. The 1986 Act requires the Home Secretary to weigh the likely adverse effects on the animals against the benefits likely to accrue as a result of the programme specified in the project licence application. In practice, it is the Home Office **Animals (Scientific Procedures) Inspectorate** which scrutinises applications, although the advisory **Animal Procedures Committee (APC)** makes recommendations on particularly sensitive applications, one of which is the primate xenotransplantation research programme. Recommendations from the Inspectorate or the APC will usually be acted upon by civil servants in the Home Office’s **Animals, Byelaws and Coroners Unit (ABCU)**, rather than actually be seen by the Home Secretary himself. The ABCU does, however, act on behalf of the Home Secretary, and it is the Minister who must take overall responsibility for the execution of the 1986 Act, even though the Secretary of State will rarely see or consider applications.

As indicated, the law states that project licence applications can only be approved if the benefits are thought to outweigh the costs to animals. This is known as the **cost-benefit assessment**, and it plays the most crucial role in the regulation of animal

experimentation. The appropriateness of this decision-making framework and the accuracy and fairness of the Home Office's judgements are controversial issues. The operation of the cost-benefit assessment in xenotransplantation procedures on primates will be a recurring and central theme of this report.

In addition to the cost/benefit approach, there are fundamental legal limits to the suffering that can be inflicted on animals in laboratories enshrined in UK and European legislation. Paragraph 5.42 of the Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 states: "The Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated." Furthermore, Article 8 of the European Directive 86/609 stipulates: "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.**" (added emphasis). As we shall see, the level of suffering endured by the primates used in Imutran's xenotransplantation research was such that the adherence of the procedures to these legislative requirements is, we assert, genuinely in dispute.

UK legislation is often claimed by proponents of animal research to be the most stringent in the world. Even if this were true, the description "least lax" would be more appropriate. For while the 1986 Act theoretically prevents the use of animals in certain circumstances, in practice it is interpreted and executed in a manner that serves the interests of the vivisection community. In a very instructive paper published in the 1997 APC annual report, the head of the Home Office Inspectorate acknowledges that the cost-benefit assessment – quantifying and balancing the suffering of animals against the uncertain 'benefits' of experimental research - is an inherently subjective affair.⁵³

The elasticity built in to the interpretation and operation of the Act has meant that powerful commercial interests have invariably prevailed over the interests of thoroughly disenfranchised animals. In the most obviously gratuitous case: How else can one explain the licensing of animal testing of cosmetics until 1998, and the continuing licensing of animal testing of household products? Apart from doubts about the reliability of such tests as a guide to safety for humans, the crucial question is: Can the "benefits" of the existence of a new lipstick or washing powder justify the deliberate infliction of pain and death on other animals?

There are other disturbing aspects of the operation of the 1986 Act. The composition of the Inspectorate is heavily weighted in favour of animal experimentation, with 17 of its 21 members being ex-vivisectionists.⁵⁴ The spectacularly one-sided report produced by the Inspectorate in response to a 1999 undercover investigation at Harlan UK (a breeder and supplier of laboratory animals)⁵⁵ destroyed once and for all any faith that

⁵³ Pp.50-60. In particular, the Chief Inspector remarked: "The assessment must still be performed by balancing 'costs' and 'benefits' which cannot be quantified in terms which allow any mathematical calculation to be performed." (p.44)

⁵⁴ A Parliamentary Question asked by Norman Baker MP and answered on 6 April 2000 says that out of 21 inspectors, 17 'have been previously licensed under the 1986 Act.'

⁵⁵ Report To Ministers By the Animals (Scientific Procedures) Inspectorate Concerning "A Report Into The Breeding And Supplying Of Dogs (And Other Animals) at Harlan UK Hillcrest. Findings of A BUAV Investigation." December 1999. (Copy in House of Commons Library.)

concerned observers may have had in the integrity and fairness of the process. There is an inherent problem relating to the conduct of the Inspectorate's work – apart, that is, from the affinities and mind-set that arise from the majority of members having previously worked as vivisectors. It is this: Any breaches or failings identified through undercover work by campaign groups or by the media frequently amount to *de facto* criticisms of the Inspectorate itself for not preventing or otherwise acting to deal with the problems so identified. Such a situation creates a potential conflict of interest and does little to engender faith in the credibility of post-exposé deliberations by the Inspectorate.

In fact, this report clearly demonstrates a feature openly admitted by the Home Office: the Inspectorate works closely with vivisectors in the crafting of licence applications. Rather than the policing role that one would imagine accompanies “stringent” legislation, the Inspectorate acts as advisor and advocate for animal researchers. Breaches of the 1986 Act are rarely considered the criminal offences that they are, licences are rarely revoked, and no prosecution of a vivisector under the 1986 Act – to the author's knowledge – has ever been undertaken.

As the government's own advisory body, the Animal Procedures Committee, has stated:

“The successful operation of the 1986 Act depends upon self-regulation by the scientific community, assisted by the Home Office.”⁵⁶

But this feature is not simply a product of the predispositions to the Inspectorate and the ABCU. The official workload assigned of the Inspectorate is unfeasibly huge. Each year **twenty-one Inspectors** are charged with:

- overseeing over two and a half million “procedures” at approximately three hundred establishments⁵⁷
- assessing carefully nearly **one thousand new project licence applications**, each of which may run to **three drafts** as the Inspectorate works to facilitate the approval of a licence application
- monitoring a further three thousand ongoing projects.⁵⁸

Each of these ongoing projects lasts an average of approximately four years, and involves a mean of some 690 animals. The monitoring process must include the crucial cost-benefit assessment, features of which are:

- Judgement on the likely severity of the adverse effects on animals;
- Standards of care and accommodation;
- Technical competence of the people and establishments to be involved in the project;

⁵⁶ Report of the Animal Procedures Committee for 1997, p.16.

⁵⁷ Report of the Animal Procedures Committee for 1997, p.26.

⁵⁸ Report of the Animal Procedures Committee for 1997, p.27.

- Relevance of the animal “model” to human condition;
- Likelihood of “success”;
- Soundness of experimental design;
- How the data generated will be used;
- Utility of the product or substance being tested;⁵⁹

Even with the best will in the world and a truly impartial approach, it would be impossible for 21 individuals to carry out these duties properly. Working from the figures above, it can be calculated that every year, each Inspector is charged with monitoring and/or assessing 180 project licences. That pans out to about **one and a quarter days per year per project**, or about **50 seconds per animal**. No wonder the notion of “stringent legislation” is viewed as a cynical myth by concerned observers.

As part of its onerous duties, the Inspectorate is expected to make visits – some unannounced - to the Designated Research Establishments where project licences take place, as well as to Designated Breeding and Supplying Establishments. Facilities in which experiments take place are often large institutions with several departments conducting several projects. On average, each Designated Establishment hosts twelve project licences involving almost 9,000 animals. Any infringements discovered by the Inspectorate must be investigated.

2.3 Primate research: regulation

Despite the above, the Government is careful *to be seen* to be giving due consideration to the interests of animals, and our society’s moral progress towards recognising the respect that should rightly fall to animals is gradually being reflected in Government policy... if in a severely attenuated fashion. Thus the Act attempts to respond to the obvious sensitivity of primates and growing concern about their use in experiments by apparently affording them special protection. Hence, it is more difficult, in theory, to gain permission to experiment on primates than it is to use pigs, sheep, rabbits or mice. (Cats, dogs and horses also enjoy relatively preferential treatment compared with other animals.) The Animal Procedures Committee (APC), which advises the Home Secretary on aspects of the operation of the Act, contains a Primate Sub-Committee and pays particular attention to project licence applications relating to their use, especially those applications that include proposed experiments classified as of “substantial severity.”

The use of “wild-caught” primates is one of the most sensitive aspects of animal experimentation today, and the government has attempted to assuage concern in this area thus:

“Under measures introduced in 1996, authority to use wild-caught primates will be given only if the applicant can establish exceptional and specific justification.

⁵⁹ Report of the Animal Procedures Committee for 1997, p.50-59.

Such cases are very rare. We must also be satisfied that the applicant has made (and continues to make) appropriate efforts to find suitable captive-bred primates. All applications to use wild-caught primates are referred to the Animal Procedures Committee for its advice.”⁶⁰

The only purpose for which the importation and vivisection of wild-caught baboons has been permitted since 1996 is xenotransplantation research.⁶¹ A recent government statement justifying the licensing of the use of *wild-caught* baboons admits: “They are extremely difficult to breed in captivity.”⁶² But, ironically, such an observation merely raises further questions about the legitimacy of *any* use of baboons. For as George Page remarks in *The Singing Gorilla*: “The fact that so many species breed only with extreme difficulty in captivity – with such difficulty that I should perhaps use the passive voice ‘can be bred’ – seems to me and others a clear indication that such captivity is emotionally traumatic.” (224) It is surely perverse that the acknowledged sensitivities of baboons should lead the Home Office to permit the acutely traumatic capture and use of wild-caught individuals rather than ban their use altogether. That it does so demonstrates that when the most vital interests of animals come into conflict with the demands of researchers, the Home Office sacrifices animal welfare rather than inconvenience vivisectioners. The subsequent analysis in this report of many aspects of the licensing of xenotransplantation research will substantiate this accusation.

Despite the extra regulatory steps to be negotiated before permission is granted for experimentation on primates, the impact of captivity and experimentation remains profound.

There are, however, definite signs of an historical sea change in attitudes. Since 1997, the Government has announced its intention not to license research on great apes (chimpanzees, bonobos, gorillas and orangutans). As there had been no such research in the UK for several years, this was an easy policy to implement (no countervailing interests to upset) with no apparent impact. The move is nonetheless symbolically important - being the first time the government has acknowledged that it would be ethically wrong to exploit, torture and kill a category of nonhuman animals, no matter what the advertised “benefit” for humans. In the same progressive vein, the chairperson of the APC, Reverend Professor Michael Banner, has expressed his personal desire to see an end to all research on primates and wishes to build a broad consensus in order to achieve just that. The APC is said to be currently exploring “how to minimise or eliminate primate use and suffering.”⁶³ Apart from challenging the Home Office’s cost-benefit assessment, we hope that this report helps to inform the debate on the issue of primate experimentation. It is hoped, above all, that it leads to a consensus in favour of a ban, on the grounds that the deliberate killing and infliction of suffering on another sentient creature, not least a close relative of *Homo sapiens*, is intrinsically immoral.

⁶⁰ Mike O’Brien MP, Written Answers, Hansard, 16 March 2000, Column 261W.

⁶¹ George Howarth MP, Written Answer No. 176, Thursday 14 May 1998. Mike O’Brien MP, Written Answers, Hansard, 16 March 2000, Column 261W.

⁶² Mike O’Brien MP, Written Answers, Hansard, 16 March 2000, Column 261W.

⁶³ Report of the APC for 1999 (London: The Stationery Office, laid before Parliament by the Home Secretary on 18 June 2000), p.18.

2.4 Summary of chapter

Baboons and cynomolgus monkeys are higher primates, a generic feature they share with humans. As such, their high levels of intelligence, complexity and sensitivity are beyond doubt, and thereby help to generate in their human kin an empathy with their suffering in Imutran's primate vivisection programme at HLS. As one major bioethics report noted: "The sophisticated capacities of primates suggest that any harm suffered by them should be given great weight."

According to the Animals (Scientific Procedures) Act 1986, the cost-benefit assessment of a proposed programme of animal experimentation is supposed to play the crucial role in the Home Office's deliberations as to whether to license such a programme, or 'project'. However, in practice, the Home Office has historically placed very little weight on the interests of animals, allowing them to be vivisected despite the doubtfulness and uncertainty of the benefits claimed by applicants to conduct animal research. The Inspectorate charged with scrutinising such 'project licence applications' is discredited for its heavy bias in favour of the wishes of researchers. In addition, the Inspectorate is grossly understaffed in relation to the volume and complexity of the work they are legally obliged to perform.

The profound ethical implications arising from experimentation on non-human primates are beginning to reshape – so far at the margins – the regulations governing animal experimentation. Vivisectors must supply extra justifications for research on primates and the acquisition of wild-caught primates. Experiments on Great Apes are currently not permitted in the UK, and there are signs of movement within the Government's advisory committee, the Animal Procedures Committee, towards a consideration of a ban on the use of all primates in research.

The evidence presented elsewhere in this report provides a unique insight into the true impact of vivisection on the animals themselves, and points to serious shortcomings with respect to the Home Office's regulation of the practice.

As well as concerns about the conduct of the two companies at the heart of this exposé (Imutran/Novartis & HLS), three fundamental questions are raised by the evidence that has been assembled:

- Can the deliberate infliction of suffering and death on nonhuman animals, not least nonhuman primates, ever be genuinely justified?
- 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?
- 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?

Index of filed documents accompanying Part I and other miscellaneous documents

I3.1 & I3.2: Fax from [REDACTED] (Imutran Ltd. [REDACTED]) to [REDACTED], 20 April 1995.

PART II

WILD-CAUGHT BABOONS IN XENOTRANSPLANTATION RESEARCH

CHAPTER 3

Acquisition, importation and captivity: welfare and biohazard implications

3.1 The importation of wild-caught baboons: [REDACTED]

Six of the 39 draft study reports for the primate xenotransplantation programme at HLS describe experiments on wild-caught baboons originating from Kenya that took place between January 1996 and March 1998. A total of 49 baboons were vivisected for these studies, which included procedures involving the grafting of transgenic pig hearts into the necks of the primates⁶⁴, into the animals' abdomens⁶⁵, and as replacements for their own hearts.⁶⁶

In answer to a Parliamentary Question tabled by Norman Baker MP (Lib Dem, Lewes), Home Office Minister Mike O'Brien reveals the use of more baboons prior to the studies for which draft reports are now available:

“Eighty wild-caught baboons were used in xenotransplantation research in 1995, 29 in 1996 and 16 in 1997, three in 1998 and none subsequently...”⁶⁷

Notice that the figure given by the Home Office for wild-caught baboons used between 1996 and 1998 is inexplicably at odds with the figure revealed by the study reports – 48 and 49 respectively.

In the same answer, O'Brien lists recent importations of wild-caught baboons:

“Twelve wild-caught baboons were imported from Kenya in 1996 for the purpose of xenotransplantation research, the earliest year for which we hold such records. A further 28 were imported in May 1999. There have been no subsequent importations for this purpose...”

The acquired documents uncover in great detail the story behind the May 1999 importation of 28 wild-caught baboons. The baboons were supplied by [REDACTED], a wildlife dealer based just outside the capital of Kenya, Nairobi. An overseas animal supply establishment must have “approved status” from the Home Office in order to supply animals for experimentation to the United Kingdom. The following extract from another O'Brien Written Answer describes the Home Office's dealing with [REDACTED]:

⁶⁴ ITN6 & ITN11: “Heterotopic cervical cardiac xenograft transplantation in baboons.”

⁶⁵ ITN19 & ITN25: “Heterotopic abdominal cardiac xenograft transplantation in baboons.”

⁶⁶ ITN9 & IAN007: “Orthotopic cardiac xenograft transplantation in baboons.”

⁶⁷ Written Answers, Hansard, 28 June 2000, Column 522W & 521W.

“The Inspectorate last visited [REDACTED] premises in Kenya in November 1995. This visit revealed that standards were not satisfactory and the Secretary of State was advised that approval of this establishment would be withheld unless and until substantial improvements were made to the accommodation and care offered to wild-caught baboons destined for supply to the United Kingdom.

By February 1997 documentary evidence confirmed that the necessary improvements had been made and the establishments “approved status” was restored. Animals destined for the United Kingdom are group-housed in large, modern outdoor enclosures. The Home Office is aware that the “sub-standard” areas remain in use for animals for supply to non-United Kingdom customers. We cannot regulate premises in Kenya used to accommodate animals that will never be shipped to the United Kingdom. Confirmation has been obtained that all animals destined for shipment to the United Kingdom have been held in the improved accommodation.”⁶⁸

Mr O’Brien omitted to mention that the “documentary evidence” had been supplied by Imutran, the very company who were keen to import these baboons into the UK for their research.⁶⁹ In any case, the acceptability of the new accommodation for UK-bound baboons at [REDACTED] premises must be disputed, not only because of the inevitable curtailment of the baboons’ natural behaviour and long-distance movement, but also because of an account of an incident related by Imutran’s own broker, [REDACTED]. The incident occurred in March 1999 in the midst of logistical problems associated with the animals’ importation:

“On top of all the problems we have had so far, [REDACTED] dropped another bombshell today. He says that he lost 4 animals this week. He explained that the metal roof of the holding cage was struck by lightning in a thunder-storm and 4 animals died as a result of the strike, leaving us with just 36 animals to select from. What more can I tell you. Can you believe this???...”⁷⁰

A subsequent communiqué faxed from [REDACTED] to [REDACTED], HLS’ [REDACTED], hints at further anticipated problems:

“, as you mention we have already paid for 40 animals and will now receive a maximum of 37. My feeling here is that this number may reduce further, dependent on how much longer the delays go on and the prevalence of thunder storms in the Nairobi area!”⁷¹

The fundamental point to bear in mind is that, no matter how many “improvements” are made to their enclosures, holding animals such as baboons in captivity will inevitably profoundly compromise their well-being and prevent them from fulfilling their complex and extensive needs and desires.

⁶⁸ Written Answers, Hansard, 16 March 2000, Column 262W

⁶⁹ See File WCB1.1 – Letter from [REDACTED], Head of the Home Office’s Animal Procedures Section, to [REDACTED], Imutran, 21 February 1997.

⁷⁰ See File [REDACTED]

⁷¹ See File [REDACTED]

The importation process appears to have commenced almost a year before the wild-caught baboons actually arrived at HLS. In June 1998, █████ submitted an application to the Home Office under the A(SP)A 1986 to “Acquire Non-Human Primates from a Non-Designated Breeding Centre for use in Regulated Procedures.”⁷² Such applications are never normally open to public scrutiny, and it is easy to see why.

The nature of the form itself suggests that the Home Office treats these applications as something of a formality: “This form shall be submitted to the Home Office as early as possible and *not less than two weeks before the expected receipt of each consignment* of primates acquired from a non-designated source.” (my emphasis)

█████ applied on behalf of Imutran for 40 baboons (*Papio anubis*) to be imported for use in Project Licence PPL 80/1223, “Xenotransplantation in Primates or Pig to Primate Heart Transplantation”, █████.

This is the reason stated by Imutran for “Seeking to Obtain Primates from a Non-Designated Source”:

“It is necessary to use either Cynomolgus monkeys or baboons for xenotransplants as it is only these species that closely resemble man with regard to their immune response. HDAF in pigs only cross reacts with a few selected primates and only Old World monkeys, great apes and man are GAL negative and thus mount the appropriate anti-GAL response. Previous experience has shown that the recipient weight is a minimum of 6 kg due primarily to the volume of blood required to prime the cardiopulmonary bypass. Purpose bred Cynomolgus monkeys of this weight are not available.”

The baboons were to be imported from “Mann & Miller” in Nairobi, Kenya. Imutran described the “details of transportation” thus:

“Nairobi to Paris CDG (█████), Paris to Huntingdon, █████ by approved carrier in a registered truck.”

Imutran stated that the “Expected Duration of Journey (From Breeding Centre to designated establishment)” was **“20-24 hours.”** And that the proposed date of arrival was **“last quarter 1998”**.

The application is signed by █████, 23.6.98.

The “Recommendation by the Home Office Inspector for the above establishment” is:

“The acquisition of non-human primates in accordance with the details supplied is approved.” (my emphasis) Signed by █████, 29.7.98.

The issue of the “the details supplied” is extremely important – not least the stated reasons for importing these animals and the estimated journey time. The accuracy of Imutran’s claim that baboons “closely resemble man with regard to their immune

⁷² See Files WCB3.1 & WCB3.2.

response” will be examined later. Meanwhile we should focus on the estimated journey time.

In a Parliamentary written answer given by Home Office Minister Mike O’Brien MP to Norman Baker MP (16 March 2000 : Column 261W-262W), it is stated:

“The total journey time for the May 1999 consignment was 34 hours from placing the animals in transport crates at the supplier’s premises in Kenya to their receipt at the designated establishment in the United Kingdom.”

This is at least 10 hours longer than the journey time estimated on the application and according to which the importation was approved.

The importation process called for the coordinated efforts of Imutran, HLS, [REDACTED] (the broker) and [REDACTED], in addition to dealings with air companies, the Home Office and the Ministry for Agriculture, Fisheries and Food (who have sole responsibility for the actual granting of the import licence, whereas the Home Office issue licences for the acquisition of the baboons for experimental purposes).

On 2 November 1998, [REDACTED] (Imutran) faxed HLS’s [REDACTED] ([REDACTED]) to confirm a request to “go ahead with the trapping of a further 25 animals to increase our holding in Kenya to 65 animals to be screened to hopefully achieve a ‘clean’ group of 40 animals.”⁷³

In addition to concerns about the trapping process itself, the capture of an additional 25 baboons would exacerbate the toll of suffering inflicted by the company’s xenotransplantation research project. Furthermore, one wonders what became of the “wasted” primates?

The ‘screening’ to obtain ‘clean’ animals refers not least to tests for Simian Herpes B virus. This virus is endemic in wild primates. But while it causes mild symptoms in these animals, in humans it frequently provokes a potentially deadly form of encephalitis - inflammation of the brain lining. The threat to health posed by Simian Herpes B is now classified by the UK Health & Safety Executive as being equivalent to notorious pathogens such as the Ebola virus and Lassa fever. The official danger-rating to humans posed by this virus was emphasised in early 2000 when more than 400 rhesus macaque monkeys at three UK wildlife parks were slaughtered after having been found to be Simian Herpes B positive. The risk posed by Simian Herpes B in primates used in xenotransplantation research will be explored in more detail below.

Imutran’s exploitation of wild-caught baboons is not limited to HLS in the UK. A fax from the company’s [REDACTED] to the primate broker [REDACTED], dated 17 November 1998, requests the latter to “supply 30 baboons, 8-12kg in weight to [REDACTED]. Animals to arrive before the year end.”⁷⁴ Imutran has an external collaborator in [REDACTED] [REDACTED] conducting pig-to-baboon organ experiments.

⁷³ See File [REDACTED]

⁷⁴ See File [REDACTED]

A series of faxes transmitted between [REDACTED] and [REDACTED] from February to April 1999 detail the complicated and troublesome logistics of importing the baboons into the UK.⁷⁵ At one stage, [REDACTED] exasperation is obvious:

“...STOP PRESS I have just spoken with [REDACTED]. [REDACTED] do not operate in Kenya but they do fly direct from Johannesburg to Madrid and then on to Paris. They also fly from Malabo (spelling?) in Guinea. Given [REDACTED] connections in [REDACTED] he feels sure they will do whatever we need to get these baboons shifted. **Surely we can get the bloody things from Nairobi to Jo’burg.** What say you?” (my emphasis)

“Do it
[REDACTED]” (handwritten note)

“Cc [REDACTED]”⁷⁶

Eventually, [REDACTED] hires a charter on behalf of Imutran that was due to leave Nairobi on the 14th May, arriving at Madrid to drop off the [REDACTED] consignment and then on to Paris.⁷⁷ Presumably, the animals would then have been driven to HLS. In the end, only 28 baboons arrived at HLS. The further decrease in numbers from 37 to 28 may have been due to some of the primates testing positive for Simian Herpes B,⁷⁸ but one cannot discount other causes such as further fatalities in the last few weeks prior to export. Indeed, one wonders what fate befell the nine disappeared baboons even if they were initially ruled out due to their viral status. Were they simply killed? Or were they released into the wild – an amazing stroke of luck for them considering the fate of their “clean” brethren? These are additional serious concerns raised by the importation process.

There are also concerns about the conditions in which baboons destined for [REDACTED] and other external collaborators may have been kept at [REDACTED] premises. According to the minutes of a “Progress Review Meeting” at Imutran on 30 March 1999, [REDACTED] held 90 baboons, 37 of which were earmarked for Imutran in the UK, with the remainder intended “ideally” for transport to [REDACTED] via Madrid.⁷⁹ Imutran were under no legal obligation to ensure that work they commissioned in Spain used baboons kept to UK standards. As the Home Office stated:

“Animals destined for the United Kingdom are group-housed in large, modern outdoor enclosures. The Home Office is aware that the “sub-standard” areas remain in use for animals for supply to non-United Kingdom customers. We cannot regulate premises in Kenya used to accommodate animals that will never be shipped to the United Kingdom...”⁸⁰

⁷⁵ See Files [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], [REDACTED], WCB14.1, [REDACTED], [REDACTED], [REDACTED]

⁷⁶ See File [REDACTED]

⁷⁷ See File [REDACTED]

⁷⁸ See Files [REDACTED] & [REDACTED]

⁷⁹ See Files [REDACTED]

⁸⁰ Written Answers, Hansard, 16 March 2000, Column 262W.

The questions are: were any of the [REDACTED] baboons kept in the “sub-standard” areas? And, if so, were these animals subsequently used in experiments commissioned by the Cambridge-based Imutran?

3.2 Baboon breeding and research in South Africa: “a unique opportunity”⁸¹

One of the faxes from primate broker [REDACTED] to [REDACTED] (15.4.99) makes an interesting reference which intensifies concerns about primate suffering: “I enclose a copy of fax from South Africa in which [REDACTED] [REDACTED] [REDACTED] makes comment about the baboon project.”⁸²

The baboon project in question is a proposal to set up a baboon breeding colony in conjunction with the [REDACTED] [REDACTED], just outside Cape Town. Intriguingly, Imutran also informed [REDACTED], a Home Office Inspector about this:

“Please also find enclosed a copy of a Fax from the [REDACTED] indicating our progress in investigating the possibilities of a baboon breeding programme.”⁸³

A document entitled “Cape Town possibilities for expanding Imutran XenoTx”, apparently produced by [REDACTED] in October 1998, sets out the goals and “strategic fit” of this option.⁸⁴ The plan outlined is to establish both a transgenic pig breeding facility and also baboon supply, quarantine and housing units at the [REDACTED]. By refurbishing existing cardiac surgery facilities and building a new “Imutran/Novartis Transplantation Research Centre” (notice the dropping of the “xeno” prefix) at [REDACTED] Cape Town [REDACTED], Imutran’s aim was to expand massively its research capabilities, allowing it to perform in South Africa 50 orthotopic cardiac pig-to-baboon transplants in 1999, followed by 50 similar experiments and 100 kidney experiments in 2000.

The strategic fit section unveils an unsettling rationale behind the South African project:

“Usage and availability of baboons is being increasingly restricted world-wide: South Africa still represents a unique opportunity”.

In a critique of the plan published in March 2000, South Africans For the Abolition of Vivisection (SAAV) note:

“Using and breeding primates for research is at the very least controversial and at odds with the increasing world-wide recognition that primates are sentient

⁸¹ See Files WCB18.1, WCB19 & WCB20.1→WCB20.12.

⁸² See file WCB14.1.

⁸³ See File WCB18.1.

⁸⁴ See Files WCB19.1 & WCB19.2.

beings that display high levels of intelligence, have complex social, emotional and family lives and are capable of suffering.”

A detailed fax dated 31 May 1999 from [REDACTED] to [REDACTED], which was presumably forwarded to Imutran, describes progress with the “[REDACTED] BABOON BREEDING PROJECT”. [REDACTED] begins by explaining the [REDACTED] is undergoing reforms, in the wake of the appointment of its first black President, in order to make it a more representative institution. [REDACTED] advises:

“Six weeks ago I received memoranda from [REDACTED] on our proposed project and amongst the points made was a clear warning to me that the ‘new’ [REDACTED] will not engage in this venture if there is a risk of adverse publicity or a run in with the animal rights groups.”

Although the aforementioned attention of SAAV may make the project less likely to go-ahead now, [REDACTED] has a contingency in any case: part of the plan to defuse opposition from “animal welfare organisations” and settle the nerves of the [REDACTED] is to portray the breeding centre as an animal welfare ‘advance’ by claiming that capturing baboons from the wild and then setting up a captive breeding colony represents progress compared to the continuous direct use of wild-caught baboons. Whatever course is followed, the animals are faced with one of two wretched fates before being vivisected: begin your life in the wild and be snatched into captivity; or spend all your days in captivity.

The presentation of a captive-breeding centre to produce baboons as an animal welfare “advance” would be a perversion of the truth. Confinement of such animals, whether originally wild-caught or not, is an inherently abusive and traumatic experience for these “cousins” of human beings. Ultimately, the establishment of such centres would subvert the increasing international recognition of the moral duty to treat such animals with respect as free individuals with basic needs that can never be expressed in captivity. If anything, captive-breeding centres entrench the prejudice that baboons are merely instruments of technology to be used and abused as their more powerful relatives – humans – see fit. Furthermore, by facilitating the supply of the animals to vivisection laboratories, it would perpetuate the suffering and death of baboons in experiments in the face of a gradual enlightenment of attitudes towards them.

In order to “win over” the [REDACTED], [REDACTED] tells [REDACTED]:

“I will need help from you and your contacts in the scientific community in the U.K.[e.g. Imutran] Europe and elsewhere and if possible from the British MRC.

What we need are letters to the President (from key persons and organisations in the International Scientific / Laboratory Animal Science community) stating that they had become aware of the [REDACTED] interest in producing capture bred baboons and wish to emphasise that there is an international need for a project of this nature and that it would contribute greatly to international co-operation etc. etc.

Austin also states that the conduct of UK projects in South Africa can be presented as a benefit to the [REDACTED]. However, the danger that South Africa and its [REDACTED] would be judged as internationally backward with regard to regulations on the use of baboons in research does not appear to have been acknowledged by the conspirators.

Despite the uncertainties, [REDACTED] is wasting no time:

“In the meantime I have started acquiring baboons and have 25 excellent breeding females. I expect to be able to acquire another 75 easily this year if I can get the show on the road. A few of the 25 are already pregnant and four infants have been born and are 4 months old and doing well.”

[REDACTED] memo⁸⁵ refers obliquely to Imutran as “the overseas partner” and stresses the need for Imutran “to obtain approval for the importation of the baboons into the UK.” A preliminary financial agreement should also be reached with “the overseas partner.” One of the project’s risks identified by [REDACTED] is the potential for market collapse after a few years – a sensible observation.

One might be saddened but not particularly surprised that the subsidiary of a multinational drug firm appears to be prepared to support such a project. What is perhaps even more disconcerting is the hint of a general sense of resentment within parts of the scientific community at regulations that might slightly mitigate some of the most extreme abuses endured by primates in research. **The grave question arises: to what extent have the following supported the proposed project which appears to be at least partly motivated by a desire to circumvent ethical restrictions on the use of baboons elsewhere in the world:**

- the “scientific community in the UK, Europe and elsewhere”;
- the British MRC (which is funded by the Department of Trade and Industry and has itself funded research into the genetic manipulation of source pigs at the [REDACTED] and;
- the Home Office?

3.3 Baboons, Simian Herpes B Virus, [REDACTED] [REDACTED] [REDACTED]

As indicated above, the baboons intended by Imutran for importation into the UK in May 1999 were tested for Simian Herpes B, with any positive animals to be discarded. Wild-caught animals are considered to pose a particularly dangerous microbiological threat.

⁸⁵ See Files WCB20.4 & WCB20.5.

A letter from [REDACTED] at the MAFF's State Veterinary Service, details the gravity of the matter. It was sent on 8 February 1999 to [REDACTED]⁸⁶ and discusses the "IMPORT OF BABOONS INTO BUILDING [REDACTED]"⁸⁷ [REDACTED] explains:

"M.A.F.F. has sole responsibility for the granting of the import licence for the above consignment, and as a consequence, must of necessity consider any risks to human health consequent upon the import and subsequent procedures."

[REDACTED] is pointed in the direction of two booklets published by the Advisory Committee on Dangerous Pathogens (ACDP), including "Working safely with Simians: Management of infection risks." [REDACTED] states:

"It has been agreed that I should review and report on your safety procedures as an integral part of the approval of the quarantine premises. I will be looking for written evidence of compliance with the guidelines issued by the ACDP."

[REDACTED] appears to be working on the assumption that the baboons will be vivisected during the quarantine period. Thus not only will [REDACTED], the pre-transplant housing area, require inspection, but [REDACTED]

"will also need to review and report on the transport arrangements for animals moving between [REDACTED] and [REDACTED], (where the procedures are to be carried out). An inspection of the facilities in [REDACTED] will also be necessary, as it is some time since our last inspection of this building, and that inspection was not done with the specific remit of considering the security of quarantined primates in the post surgical phase."

The extent of the risk is highlighted by the fact that expert advice was obtained by MAFF from Dr [REDACTED] of Porton Down, the chemical and biological research establishment which houses some of the most dangerous pathogens known to humanity. The key point to have emerged from MAFF's discussion with [REDACTED] is that "The major risk is from Simian Herpes B Virus, which can be fatal in humans." [REDACTED] comments:

"You may be aware that a fatality from Simian Herpes B Virus has been reported in an American Laboratory Worker, following conjunctival [eye] contamination during weighing procedures..."

[REDACTED] stipulates that at least two tests for the virus, with a minimum gap between them of two months, must take place once the baboons arrive at HLS. However,

"Seronegativity is not an absolute guarantee of freedom from infection. Bearing in mind that these animals will be undergoing immunosuppression prior to transplantation, everyone should be made aware of the risks of the activation of a latent herpes B infection."

⁸⁶ Curiously addressed to him at HLS rather than at Imutran.

⁸⁷ See Files WCB21.1→WCB21.3

Thus there is an intrinsic level of risk involved with the importation and use of wild-caught baboons. Furthermore, the aforementioned American incident demonstrates the relative ease with which Simian Herpes B Virus can be transmitted: the monkey had thrown faeces in the face of the lab worker. [REDACTED] advises that “Use of eye protection is therefore a necessity.” One wonders, however, what precautions were taken by those handling the baboons before they reached HLS, such as [REDACTED] workers, the packers of the animals in Nairobi and the handlers at Charles De Gaulle airport?

In normal circumstance, the risk would only be posed to those who were directly involved with handling the monkeys. But the xenotransplantation experiments pose a unique problem, one outlined in [REDACTED] letter:

“I recommend that you discuss with your medical officer, and with the transplant surgeons, the procedures to be followed following any needle stick injury, or any other incident with the potential to transmit infection of Herpes B. These procedures must be written and agreed by all parties. **It is necessary to bear in mind that the transplant surgeons may well be working on immunosuppressed human patients**, and it may therefore be advisable for them to enter into discussions with their hospital’s Infection Control Officer.” (my emphasis)

What’s more, the highly invasive nature of the xenotransplantation procedures would appear to present a relatively dangerous situation with regard to incidents “with the potential to transmit infection of Herpes B.”

At this point, one needs to consider the broader picture with regards to the use of wild-caught baboons in Imutran’s xenotransplantation research at HLS. MAFF’s considerations and recommendations are being made in February 1999, in time for the May 1999 importation. However, 49 baboons had already gone under the knife between 1996 and 1998, in addition to eighty that were used in 1995. The Home Office are on record as declaring that 12 wild-caught baboons were imported into the UK during 1996, the first year that such records were supposedly kept. In addition, at least one large importation of wild-caught baboons must have taken place prior to 1996. Given the tone and language of [REDACTED] handwritten comment on MAFF’s letter (“It now seems...”) and the thoroughness and sense of a fresh approach conveyed in MAFF’s letter to [REDACTED] [REDACTED], it is reasonable to question the adequacy of the approach to health and safety for these earlier importations and procedures.

Furthermore, blood and tissue samples from transplanted baboons were sent to various laboratories. One fax, dated 23 October 1996, from Imutran to HLS, complains about the late arrival of blood samples that were **transported by taxi** from HLS to Imutran.⁸⁸ Other documents refer to couriers transporting material. What infection control procedures were in place during these movements of potentially biohazardous substances?

⁸⁸ See File HLSAPP4A.1

Further questions follow from a document headed “Pre-surgery Anti-pig Antibody titres in baboons.”⁸⁹ It appears to have been generated by [REDACTED], Imutran’s then [REDACTED], on 6 March 1998. It raises two issues of importance. The first, regarding a failure to measure the level of anti-pig antibodies in baboons before surgery, is important enough in itself and will be dealt with in a subsequent section. The second amounts to this:

[REDACTED] states “7 had no-preAB titres-samples **and must not be worked on due to positivity for Herpes B.**” (my emphasis) [REDACTED] responds in a handwritten added comment: “[REDACTED] I can not believe we did 7 transplants without pre transplant antibodies.” Looking beyond [REDACTED] concentration on the anti-pig antibody issue, we see in the wording the possibility that 7 herpes-B positive baboons were transplanted in late 1997/early 1998 at HLS as part of Imutran’s xenotransplantation programme.

In this regard, it’s worth reflecting upon the concerns expressed by [REDACTED] (MAFF) and [REDACTED] (Porton Down) about transplant surgeons potentially going on to work on immunosuppressed patients. Given the possibility – as implied by this document – that surgeons engaged in the xenotransplantation project at HLS have been working on Herpes B-infected baboons, a series of important questions follow: who were these surgeons, did they conduct transplant operations on humans afterwards and, if so, what infection control precautions were in place at the time?

[REDACTED]

The above evidence points to the possibility of a major health risk having been posed to transplant patients [REDACTED]. Ultimately, only an independent inquiry into this and other incidents highlighted by this report can uncover the whole truth. We urge that such an inquiry be urgently initiated by the Government.

3.4 The ‘disappeared’

According to a Written Answer issued 28 June 2000 by Home Office Minister Mike O’Brien MP:

“Twelve wild-caught baboons were imported from Kenya in 1996 for the purpose of xenotransplantation research, the earliest year for which we hold such records. A further 28 were imported in May 1999. There have been no subsequent importations for this purpose...”⁹⁰

There is, however, a perturbing discrepancy between the Home Office figures for importations of wild-caught baboons and the numbers revealed by the study reports.

⁸⁹ See File WCB22.1

⁹⁰ Written Answers, Hansard, 28 June 2000, Column 522W & 521W.

While the Home Office maintains that **only 12** wild-caught baboons from Kenya were imported in 1996, the study reports reveal that **between 36 and 41** baboons arrived from Kenya on 14 April 1996.

3.5 Time in captivity

One of the reasons for such serious concern about the use of wild-caught primates in research is the trauma they are likely to experience as a result of unfamiliar close confinement. In the wild, baboons will forage for a wide variety of food and cover at least five to eight kilometres a day.

The following telling observation comes from HLS' [REDACTED] in a letter to Imutran sent late June 1999, approximately **6 weeks** after the latest importation of wild-caught baboons:

“The ethical considerations surrounding the capture of wild baboons means we all have a responsibility to ensure that these animals do not spend unnecessary time in what must seem to them to be small enclosures.”⁹¹

We shall return to this document shortly, but for the time being it is important to note that deep ethical concern is being raised by HLS themselves about keeping wild-caught baboons captive for a planned period lasting up to **seven months**.

In fact, the life/death histories of the baboons used in the studies reveal that many of them spent a great deal longer than seven months in captivity before being killed.

Study ITN19 consumed 22 animals who all arrived on 14 April 1996. The transplants took place over a long period of time, between 9 October 1996 and 6 March 1997, resulting in captivity periods of **between six and 10.5 months**.

The ordeal endured by the 5 female baboons eventually used in study ITN25 was even longer. Having also arrived on 14 April 1996, three of them went under the knife on 13 March 1997, with the remaining two on 6 May 1997: a period of **over one year in captivity**.

The greatest hardship must have been experienced by the six baboons who died for study IAN007. Having been operated upon between 17 November 1997 and 23 March 1998, these unfortunate animals had spent **between 19 months and nearly two years in captivity**.

We must bear in mind that all animals (not least our close primate relatives) are susceptible to psychological distress and suffering in addition to actual physical pain. The deprivation experienced by these baboons – snatched from the wild and held captive in some cases for up to two years – must have been particularly severe. Their prolonged suffering and miserable deaths are some of the most scandalous revelations of this report.

⁹¹ See File WCB26.1.

Before we explore the fate of the baboons in the actual experiments, the fate of the 28 baboons imported in May 1999 needs to be examined.

3.6 What happened to 'The HLS 28'?

██████████ of HLS told Imutran in his June 1999 letter that the baboons should be used as quickly as possible, not only because of the ethical concerns about keeping these animals captive, but also in order to honour their "commitment to the Home Office."⁹² The letter does not spell out exactly what that commitment was, but one can reasonably deduce that it pertains to the swift use of the baboons, by the end of 1999 at the very latest.

And yet none had been operated on by the end of the year. The company's six monthly report to the Home Office for the second half of 1999 states categorically: "There have been no transplants performed during this reporting period."⁹³

More confusingly, Home Office Minister Mike O'Brien told Parliament in a June 28, 2000 Written Answer that while 28 wild-caught baboons were imported for xenotransplantation research the month before ██████████'s letter (in May 1999), no wild-caught baboons had, in fact, been used in such research since 1998. O'Brien also said:

"There are no cynomolgus macaques or baboons known to be awaiting xenotransplantation procedures at the present time in United Kingdom designated establishments."

What, then, happened to the 28 wild-caught baboons - if they have not been used and are not awaiting the xenotransplantation procedures for which they were imported? One had already "disappeared" by the end of 1999, when Imutran told the Home Office: "At present we have twenty-seven baboons imported under Home Office Licence PPL 80/1223 awaiting heart transplantation."⁹⁴

Could it be that the group was transferred to another project at some point during the first half of 2000. This would, however, appear to be at odds with the conditions of their importation – notwithstanding the special pleading that resulted in an import licence being granted expressly for xenotransplantation research? Or could they have been despatched to one of Imutran's non-UK collaborators? A third option is that they were simply killed - unused. Needless to say, because of the serious ethical and regulatory concerns, an answer is urgently required.

⁹² See File WCB26.1.

⁹³ See File WCB24.1.

⁹⁴ See File ██████████

3.7 Summary of chapter

This chapter has raised concerns in the following areas:

- The suffering endured by baboons throughout the acquisition process: the trapping, captivity and the lengthy transportation to research laboratories in the UK and Spain.
- The Home Office's endowment of 'approved status' for [REDACTED] baboon supply establishment solely on the basis of evidence supplied by the prospective importers, Imutran.
- The safety and welfare of UK-bound baboons at [REDACTED] premises, especially in the light of four deaths caused by a lightning strike during a thunderstorm.
- The journey time for the importation of "the bloody things" – 34 hours – in contradiction to an application for their importation submitted by Imutran to the Home Office which stated an estimated journey time of 20-24 hours.
- The holding conditions of wild-caught baboons procured for Imutran and destined for xenotransplantation research in [REDACTED].
- The fate of baboons who were never shipped out for experimentation from [REDACTED] Kenyan establishment. Did they die (as a result of, e.g., lightning strikes, disease, etc.) or were they destroyed in captivity if they were deemed unsuitable for vivisection?
- Imutran's apparent interest in a baboon breeding and research facility in Cape Town, South Africa. The project could have circumvented increasing, ethically-based, restrictions worldwide on the use of baboons in research.
- The involvement the following might have had in the development of the South African baboon breeding programme: the Home Office, Medical Research Council, and the scientific community in the UK and elsewhere.
- The risk to the general human population posed by the Simian Herpes B virus, which is widespread in wild-caught baboons.
- The particular risk to transplant patients [REDACTED] that might have resulted from [REDACTED] transplant surgeons being involved in vivisectioning baboons.
- The potential threat to human health posed by primate blood and tissue samples being ferried around by taxi.
- The apparent discrepancies between Home Office figures and HLS study report data as to the numbers of wild-caught baboons imported since 1996.
- The possibility that wild-caught baboons have suffered the trauma of capture, captivity and importation into the UK, without then being subjected to

subsequent experimentation. In welfare terms, it would be to the animals' benefit to have avoided the experiments. However, from a regulatory perspective, permission was granted for them to be imported on the basis of the excuse that they were vital for xenotransplantation research.

- Despite the serious ethical concerns about keeping wild-caught baboons in captivity, 31 baboons appear to have spent between 6 months and two years at HLS between April 1996 and March 1998.
- The apparent breaking of a commitment made by Imutran to the Home Office that 28 baboons imported during May 1999 would be used by the end of the year at the latest.
- The recorded 'disappearance' of one of the 28 and the mystery as to what happened to the others.

CHAPTER 4

Research on baboons

Perhaps the most significant aspect of the documentation that is the source of this report is the unparalleled insight it gives into the fate of the animals who have been forced to endure xenotransplantation experiments. No longer is their suffering a matter of conjecture or disputable. What we have before us are the observations direct from the researchers themselves. Later we shall examine what happened to the 424 cynomolgus monkeys sacrificed during the reported studies. For the time being we shall scrutinise the baboon experiments.

Each of the study reports describes in detail the housing conditions, the surgical procedure and the dosing regimen to which each primate was subjected. Appendices are also attached to each report and these record information relating to food and water consumption, urine output, blood biochemistry and haematology, as well as the raw clinical signs for each individual animal. Additional knowledge about some of the studies can be gleaned from other documents now exposed as well as published scientific papers.

The baboons endured three different types of experiment at HLS, and we shall examine each in turn. However, one early study, ITN1, is not reported. It took place in 1995, and is mentioned in the study report for ITN6:

“In an initial study (ITN/1), donor hearts from cynomolgus monkeys were heterotopically transplanted into the neck of baboons.”

Given that the research conducted by Imutran has aimed to develop *pig* organs for xenotransplantation, we regard this study as particularly gratuitous. No document refers directly to the number of baboons used in this study, but information contained in Home Office Minister Mike O’Brien MP’s Written Answer on 28 June 2000 is unsettling: he says that eighty wild-caught baboons were used in xenotransplantation research in 1995. Given that no other study report refers to the use of baboons before 1996, and we are unaware of any other xenotransplantation research programme that has used such animals, we can only presume that the eighty baboons were slaughtered for this “developmental”⁹⁵ study: more than all the other wild-caught baboons used in the UK since that study. If this presumption is confirmed to be accurate, then this study may represent the most terrible episode in the whole affair.

4.1 Heterotopic cervical cardiac xenograft transplantation in baboons

Studies ITN6 and ITN11 investigated “**Heterotopic cervical cardiac xenograft**

⁹⁵ See File HLSAPP2.5.

transplantation in baboons.⁹⁶ Each used three monkeys and took place during January-March 1996 and July 1996 respectively.

Here, “**heterotopic cervical cardiac xenograft transplantation**” means, in actuality, the transplantation of transgenic pig hearts into the necks of baboons. The introduction to both study reports sets the scene:

“In an initial study (ITN/1), donor hearts from cynomolgus monkeys were heterotopically transplanted into the neck of baboons. This study demonstrated the suitability of this model in terms of surgical simplicity and subsequent ease of monitoring of cardiac activity.”

The aims of the studies were twofold:

- to investigate whether Imutran’s transgenic pig hearts would resist hyperacute rejection (HAR) when transplanted into baboons;
- to see whether subsequent rejection processes could be inhibited by a regime of immunosuppressive drugs

The transgenic pig hearts were not life-supporting in these studies - the baboons’ own hearts were left in place. The studies were thus merely investigating the rejection of the pig hearts rather than whether they could also perform the necessary functions to sustain life in the baboon.

Imutran gained Home Office permission to use baboons (and cynomolgus monkeys) by arguing that these primates were good ‘models’ of human beings. In particular, the company insisted that they would be the ideal test bed to determine whether pig organs from animals manipulated to express the human anti-rejection protein called hDAF, would be accepted rather than destroyed by the human immune system. It is the presence of human hDAF in the pig organ that is supposed to suppress a key aspect of the human immune system known as **complement** – complement being the feature supposedly responsible for triggering hyperacute rejection (HAR).

This debatable premise of sufficient baboon/human similarity will be examined in more detail later. In the meantime, we shall focus on the costs to the baboons.

All of the baboons used in the 39 studies described in the acquired documents were captured from the wild in Kenya before being shipped to HLS. The four male and two female baboons used in the studies under discussion (ITN6 and ITN11) were all estimated to be between two and four years of age – mere juveniles.

Having been sedated and anaesthetised, the “donor”⁹⁷ piglets – just 7-21 days old - were split apart along their breastbone to expose their organs, and held open by

⁹⁶ See Folder ITN6-972924.

⁹⁷ HLS and Imutran use the term “donor” to describe the pigs from whom the organs are removed. However, in the Nuffield Report, which concluded that the use of pigs for xenotransplantation could be ethically acceptable: “The term **source animal**, rather than **donor animal**, has been used in recognition of the fact that an animal has no choice in whether its organs or tissue are removed for human use.” (p.11) The Kennedy report followed this thoughtful example.

retractors. Having cleared the way for the removal of the heart, the piglets were killed as the heart was stopped with a cardioplegic solution and the main veins to the heart cut to drain the animals' blood away. With all the necessary veins and arteries severed, the porcine heart was transferred to a bowl to be prepared for implantation into the baboon neck, leaving the piglets a dismembered, bloody mess.

The recipient baboons were sedated and anaesthetised. The piglet hearts, weighing between 20.9 grams and 27.1 grams, were implanted into a pocket created under the skin of the neck. Each baboon's jugular vein was connected to the grafted heart as part of the process for linking the organ to the baboon's blood supply. If and when the porcine heart started to beat stably, the wound was sewn up, the baboon was allowed to recover from anaesthesia and returned to his/her cage in the [REDACTED].

After the surgery a painkiller was administered to the animals. Anti-emetic treatments were also used to try to ameliorate the nausea and vomiting caused by the toxic doses of immunosuppressants.

All the baboons used at HLS in the reported studies were kept individually in stainless steel and "printboard" cages measuring only 78 cm wide, 103 cm deep and 230 cm high – about the size of a toilet cubicle. The cages included a so-called squeeze back system. This allows the back of the cell to be moved forward and the inmates simultaneously to be thrust against the front of the cage. Drugs and blood samples can then be administered more easily. Wood chippings were provided as both litter and a foraging material.

The baboons were generally fed on a dry diet. The best they could hope for was this:

“Wholemeal bread and fresh fruit or vegetable produce was sometimes offered in order to enrich the environment and improve the interaction between the animals and their handlers.”⁹⁸

One of the central aims of these studies, and indeed the whole programme of research, was to try to prevent post-hyperacute rejection of the xenotransplant through the administration of an **acceptable** immunosuppressive regime – i.e. not too toxic or likely to leave the animal susceptible to opportunistic infection.

The records show that this problem has remained intractable. The three baboons used for study ITN6 were heavily immunosuppressed with a combination of [REDACTED], [REDACTED] and [REDACTED]. The three used in Study ITN11 were also dosed with another immunosuppressant, [REDACTED].

The hazards of the immunosuppressives are spelled out in the study report's discussion of “Terminal studies”. Both “opportunistic infection” and “drug toxicity” arising from the immunosuppressive treatment are listed as potential reasons for “sacrifice” of the baboons.

⁹⁸ See file ITN6-972924, p.12.

The standard pattern of dosing included [REDACTED] administration of [REDACTED] by oral gavage, a procedure involving the insertion of a catheter into the stomach via the mouth. [REDACTED] were also administered by the same method once a day. The baboons also received [REDACTED] [REDACTED] by oral gavage. In Study ITN11, [REDACTED] was administered by oral gavage the day before transplant. Four blood samples were taken from the baboons three times a week.

So, what did this all mean for the animals?

In study ITN6, baboon **V683m** was transplanted on 15 January 1996. He was killed 13 days later. By day 4, his 'Clinical Signs' record read as follows:

Am: Quiet and huddled, subdued but marginally brighter. No movement. Loose faeces.
Pm: Quiet and huddled. No movement. Loose faeces. . Neck still swollen.

On day 8:

Am: Quiet but alert. Dried blood around both nostrils.

His extra, implanted heart stopped beating at nine o'clock on the evening of the thirteenth day. It was time for his lethal injection.

5 February 1996 was the date for vivisection on baboon **W205m**. Like his predecessor, he was quiet throughout his last days. The grafted organ started to beat "satisfactorily", though through day 4 to 5 his neck was swollen and vomit lay on the floor of the cage. On day 11 things went from bad to worse:

Quiet but alert. Occasionally huddled.
Quiet and huddled. Transplanted heart seems very large and possibly discomforting animal. Neck swollen.

And subsequently:

12	am	Quiet and huddled. Holding neck. Appears unsteady.
	pm	Quiet and huddled. Holding neck. Appears unsteady.
13	am	Quiet and huddled. Holding neck. Appears unsteady.
	pm	Quiet and huddled. Supporting neck with left arm. Unsteady when moving.
14	am	Quiet and huddled. Transplanted heart swollen and red, seeping yellow fluid.
	pm	Quiet and huddled. Transplanted heart swollen and red, seeping yellow fluid.
15	am	Quiet and huddled. Transplanted heart appears swollen. Yellow fluid around swelling.
	pm	Quiet and huddled. Transplanted heart appears swollen. Yellow fluid around swelling.
16	am	Quiet and huddled. Transplanted heart appears swollen. Animal picking at transplant site. Yellow fluid around swelling.
	pm	Quiet and huddled. Transplanted heart appears swollen. Animal picking at transplant site. Yellow fluid around swelling.

This was his harrowing condition for the last 48 hours of his life:

20	am	Quiet but alert. Scab on operation site appears clean and dry. Keeps holding area where transplanted heart is.
	pm	Quiet and huddled. Little movement and unsteady when moving. Showing signs of discomfort.
21	am	Quiet and huddled. Scab on operation site appears dry. Reluctant to move. Marked firm swelling around implant. Animal showing obvious discomfort. Fluid swelling developing in sub-mandibular region.
	pm	Sero-sanguinous fluid drained but no purulent material. Transplanted heart beat barely palpable. Swelling so large animal sacrificed for humane reasons.

The clinical signs suggest that this primate was suffering substantially for at least 10 days before he was put out of his misery.

At this point, before recounting the fate of the third animal in this study, it is important to outline an additional important aspect of the regulatory legislation for animal experiments that appears to be pertinent to the experience of **W205m** and other animals used in Imutran's xenotransplantation research.

Each licensed study has a '**severity limit**' attached to it that "represents the worst potential outcome for any animal subjected to the protocol [i.e. procedures which make up the design of the study], even if it may only be experienced by a small number of the animals to be used."⁹⁹ There are three bands of severity: **Mild**, **Moderate** and **Substantial**. The severity limit on a study is intended to curtail the amount of suffering that can be inflicted on an animal. Indeed, the severity limit should not even be **approached** unless it is deemed "absolutely necessary to meet the specified objective" of the study.¹⁰⁰ The regulations also contain the significant claim that "the Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated." European legislation also bans, in theory, the infliction upon animals of "**severe pain, distress or suffering**."

Thus, the apparent intensity and the duration of the suffering endured by animal W205m raises the question of whether his pain and distress exceeded the severity limit that would have been set as a condition on the license for this study. Whichever way this question is answered, this episode provokes deep concern.

If the severity limit was indeed exceeded, then the Home Office Inspector should have been notified and/or the animal euthanased. If the Home Office was not notified promptly then the conditions of the project licence would have been breached. Legal responsibility for compliance with the severity condition ultimately lies with the project licence holder (in this case, Imutran's Dr [REDACTED]), although the personal licensee who is entrusted with ensuring the proper on-going monitoring of animals must notify the project licence holder if the severity limit is likely to have been, or be, exceeded.

Alternatively, *if the severity limit was not exceeded*, then it had clearly been set too high by the Home Office to offer the protection to severely suffering animals promised by the legislation.

In summary, the suffering undergone by W205m raises profound questions about this experiment's level of adherence to the legal severity limit placed upon it, and/or the effectiveness and appropriateness of the manner in which the Home Office has regulated this study and the research programme as a whole.

⁹⁹ Guidance on the Operation of the Animals (Scientific Procedures) Act 1986: para. 5.41.

¹⁰⁰ Guidance on the Operation of the Animals (Scientific Procedures) Act 1986: para. 5.43.

Baboon **W201m** survived only two days post transplant, which is probably a blessing when we consider the fate of his forerunners. Nevertheless, his demise was intensely traumatic:

1	am pm	Quiet and huddled. Reluctant to use left leg. Transplanted heart beat just palpable. Quiet, sitting on cage floor. Transplanted heart beat very faint and swelling in neck still considerable. Some seepage of blood from wound (17.20). Lying on cage floor, uncoordinated limb spasms for approximately 30 seconds, then sits up and appears alert and normal again (22.45).
2	am	Very quiet, with limited use of left side. Sacrificed for humane reasons.

Study ITN11, which took place during July 1996, was an unmitigated disaster: “all animals were sacrificed whilst either still under general anaesthesia or shortly after return to the animal unit.” These botched operations are referred to as “Technical Failures”: so much for the “surgical simplicity” of this “model”. These “technical failures” are another prominent and repetitive feature of the entire primate research programme.

One of the most fundamental issues to emerge, not only from these experiments, but also from the whole research programme, is the application by the Home Office of the pivotal cost-benefit assessment, as described earlier in section 2.2. The importance of this theme cannot be overstated, and it is a recurring motif throughout this report.

As we have seen, the “costs”, in terms of suffering and deprivation, endured by these higher primates over a period of several months was intense and protracted; from capture, captivity, transportation, quarantine and incarceration at HLS, ending in the experiments themselves.

Although we believe that no potential benefit could possibly justify such treatment, the Home Office is charged with assessing the potential positive outcomes of such procedures to see if they outweigh the costs. The most obvious point to make in this respect is that four years and some four hundred higher primates later Imutran appear to have made very little progress, if any, towards clinical trials of hDAF pig hearts or kidneys, never mind establishing xenotransplantation as a successful and widely available treatment for organ failure.

In deciding on whether to grant a project licence, the Home Office is also supposed to take into account **the technical competence of the people and establishments to be involved in the project, the likelihood of “success”, the soundness of experimental design and how the data generated will be used**. Given the conduct and outcome of these experiments, it seems incredible that they could have been permitted on cost-benefit grounds.

4.2 Heterotopic abdominal cardiac xenograft transplantation in baboons

The main difference between these studies and those described in the previous section was that the piglet hearts were grafted into the baboons’ abdominal cavity rather than

into their neck. A surgical incision was made into the cavity and the organs (abdominal viscera) were moved aside to expose the major blood vessels below the renal (kidney) arteries. The pig heart was then attached to these exposed vessels. Once again, the object of these experiments was to investigate the rejection of the organ and test immunosuppressive regimes rather than to discover whether the pig heart could sustain life in the baboon – the baboons' own hearts were left in place.

The first of the two studies was **ITN19**, which consumed 22 wild-caught baboons between October 1996 and May 1997. The immunosuppressive regime was similar to that intended for the disastrous study **ITN11**, [REDACTED] by oral gavage as the study progressed. One transgenic heart survived an unusually long time: 99 days. However, an Imutran document¹⁰¹ reveals: "This requires oral doses which are about eight times higher than in a human being," though it claims "this regime was well tolerated by the animals."

There were six "technical failures" according to the study report. But in a separate document – a table entitled "Use of Baboons in Comparative IS Study" – conflicting information is presented.¹⁰²

- One of the animals whose procedure was recorded as a technical failure, **X223m**, is actually listed in the table as having died after 3 hours when the grafted pig heart suffered hyperacute rejection.
- The demise of **X222m**, who collapsed and died after one day (deaths before 24 hours are classified in the study reports as technical failures), is described in the table as a technical failure, but not in the study report:

pm	Quiet but alert, sitting on perch. Died suddenly at 11.40 pm.
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At least two of the 22 animals used in this study did not make it out of theatre. **X237m** "died on table"¹⁰³ and **X232f** was sacrificed while still under anaesthetic due to "Primary non function of graft." Of the remaining animals, **X230f** died because "the heart did not contract; pig too young;" **X236f** was destroyed within a day due to "Poor initial contraction – primary graft failure." One more animal died very quickly: **X227m** is said to have been sacrificed when the graft stopped beating due to hyperacute rejection 12 hours after the operation, though the study report lists him as surviving one day:

Lying on front across perch, no movement, eyes closed. No faeces seen. Transplanted heart stopped beating. Sacrificed.
--

Baboons **X241m**, **X214f**, **X217m** & **X204f** all died after four to five days due to "acute vascular rejection" (AVR) of the grafted heart. (AVR will be discussed in more detail later in the report.) **X214f** had a particularly hard time:

¹⁰¹ See File [REDACTED]. This document may well have been intended for submission, or be a draft of such a document, to a Home Office Inspector, as it is entitled: "Programme for the use of the 9 remaining baboons at HLS under the authorities of PPL80/848."

¹⁰² See File WCB29.1.

¹⁰³ See File WCB29.1.

Day 2, pm: Quiet but alert, resting against cage front, moves when approached. No faeces seen.

Day 4, am: Quiet and huddled, pale mucous membranes, sitting on cage floor, appears weak when moving. Abdomen appears slightly swollen. No faeces seen.

Day 5, am: Collapsed on cage floor. Abdomen swollen and appears fluid filled. Salivating. Very laboured breathing. Extreme difficulty trying to walk. Pale mucous membranes. Loose faeces. Sacrificed for humane reasons.

According to the table, she had suffered a “cerebral incident.”

X231m and **X226f** survived slightly longer – 15 and 12 days respectively – before both succumbing to AVR. X231m had been vomiting during the first week, and the wound became swollen with a fluid build-up. In the last few days of his life the drugs seemed to have taken their toll: he vomited and was “very unsteady” after dosing. X226f was predominantly quiet throughout her twelve days before she was killed when the heart stopped beating.

X229m was destroyed after the graft became infected and stopped beating. This was the story of his last two days:

9	am	Subdued. Salivating pre and post dosing. Slightly dehydrated. Liquid faeces.
	pm	Quiet and huddled. Salivating. No faeces seen. Transplanted heart beating well.
10	am	Very subdued, heavy lidded, inactive even when stimulated. No faeces seen.
	pm	Transplanted heart stopped beating. Sacrificed.

The operation site of **X200f** broke down after two days and had to be repaired under general anaesthetic. The next day she was found with a large protrusion coming from her wound. Until she died after 19 days, she was mostly quiet and huddled, suffering from diarrhoea and was observed to be shivering one day. Puffiness and swelling under the eyes indicated the toxic effects of the drug regimen. Her last two days were horrific:

18	am	Quiet and huddled, occasionally alert, very pale. Sitting on perch, reluctant to move and appears slow and weak when moving. Swelling under both eyes. Abdomen appears swollen, wound weeping. Normal faeces.
	pm	Rectal temperature 38.2°C.
19	am	Quiet but alert, occasionally huddled. Reluctant to move, appears weak when handled. Abdomen appears swollen, large abdominal wall abscess. Slight swelling under both eyes. Loose faeces.
	pm	Sacrificed for humane reasons.

X225m was euthanased after 15 days because of an infected haematoma, or swelling caused by clotted blood. On day 3, a “large volume of bloody mucoid faeces” had been observed. By day 9 his right arm had become swollen around an injection site, and on day 11 the arm was badly swollen and bruised. Eventually:

12	am	Quiet but alert. Right arm still swollen, skin broken and oozing blood.
	pm	Quiet but alert on perch. No faeces seen. Transplanted heart beating.
13	am	Quiet and slightly huddled. Right arm swollen.
	pm	Quiet and huddled. Right arm swollen with large open wound, heavily bruised, not bleeding. Vomit during dosing. Transplanted heart beating.
14	am	Quiet but alert, sitting at front of cage. Slow movement. Large open wound on right arm, discharging pus. Normal faeces.
	pm	Quiet but alert, moves when stimulated. Wound on right arm larger than observed earlier.
15	am	Quiet and huddled, sitting on perch. Reluctant to use right arm. Further wound breakdown. Sacrificed for humane reasons.

The remaining five baboons lived a relatively long time: 26, 32, 37, 44 and 99 days. For the most part, these animals alternated between quiet and alert periods, with bouts of vocalising, vomiting and diarrhoea, until they were killed when the grafts stopped beating due to another rejection process, cellular rejection.

X207m certainly appears to have suffered quite substantially during his 26 days of life post-transplant:

13	am	Quiet but alert, slightly active. Profuse liquid faeces, shows abdominal discomfort.
22	pm	Quiet but alert, sitting on perch, reluctant to move, active if stimulated. Transplanted heartbeat feels faint.
	am	Quiet but alert, sitting on perch, moves slowly if stimulated.
	pm	Quiet but alert. Bloody discharge from penis.

X211m was “retching and salivating” on day 5 of 32. For the most part he was quiet and subdued until his condition appears to have deteriorated during the last week.

X240f survived a remarkable 99 days. For the last three weeks however, her condition appears to have been particularly poor, as she grew weaker and developed muscle tremors. By day 92 she was “exhibiting discomfort when moving, especially right leg.” Three days later, body and head tremors were noted. On day 94 she was not dosed in error. She seems to have been barely inclined to move during these last few days until she was finally euthanased on the morning of day 99. According to a published paper referring to this animal (see below), she was killed “due to persistent pyrexia [fever].”

Imutran wrote up this experiment for publication in the journal Transplantation Proceedings, 31, 958 (1999). The paper, entitled “Three-Month Survival of HDAFF Transgenic Pig Hearts Transplanted Into Primates,” () tells an interesting version of events compared to the study report and table. The paper actually compares the survival of transgenic pig hearts with non-transgenic pig hearts. The latter study is ITN25, which will be discussed shortly.

The paper refers to only nine heterotopic abdominal transgenic heart transplants, with a minimum survival of ten days ranging up to 99 days. The nine transplants referred to coincide with the ten longest survivors in the study – X200f is the only relatively long survivor not to receive a mention. All of these ten, however, received () on day 2 or 3 relative to the shorter survivors. The estimated six technical failures are omitted, as are the four animals who survived four to five days before succumbing to AVR.

The two operations listed in the table referred to above as ending in hyperacute rejection also fail to make an appearance. However, in the paper, Imutran claim: “No hDAF transgenic pig heart underwent hyperacute rejection (HAR).” Although this is true for the nine procedures focussed upon in the report, the recorded incidences of HAR in the remaining procedures do appear to be significant findings, for if the transgenic organs do not reliably quell HAR then another fundamental question mark hangs over the viability of Imutran’s hDAF organs.

Imutran also stated in the Transplantation Proceedings paper:

“We have developed an immunosuppressive strategy... that allows prolonged xenograft survival while being well tolerated by recipients.”

An examination of the clinical signs of these animals in conjunction with the haematology and biochemistry readings contained in the study report throws this assertion open to serious question.

The aforementioned study **ITN25** (March→May 1997) was a control study using non-transgenic pig hearts. The baboons would not have been expected to live long because of the probability of immediate hyperacute rejection of the non-transgenic organ. In the event, the longest survival period was ten days, with the by-now-familiar range of clinical symptoms. **X198f**'s experience was particularly grim:

1	am	Quiet and huddled, sitting on perch. Normal faeces. Sudden collapse, sitting on cage floor, reluctant to move, weak pulse and pale colour. Transplanted heart beating irregularly.
	pm	Quiet and lethargic, sitting on perch. Transplanted heart beating slowly and weakly.
2	am	Quiet, unusual posture, slow movement, unsteady when stimulated, weak when handled. Frank haemorrhage from abdominal wound (possible slow haemorrhage from anastomosis). No faeces seen. Transplanted heart beating slowly and weakly. Sacrificed for humane reasons.

4.3 Orthotopic cardiac xenograft transplantation in baboons

These procedures were, in an important sense, the most drastic of the three types inflicted on baboons, notwithstanding the grotesque concept of implanting a piglet's heart into the primates' necks. “Orthotopic” describes the transplantation of the pig heart into the position in the baboon where the heart would normally be located. As such, the procedures involved the complete replacement of the baboon's own hearts with that of the pig's with the aim of investigating how effectively the grafted organ could support life in the baboon. If the graft started to fail because of rejection or some other complication, deterioration and death would be swifter and harder to manage than in the heterotopic model. Baboons were chosen as the test recipients because their larger size compared to cynomolgus monkeys supposedly made the surgical procedures easier.

This surgical procedure was severe and lasted on average almost four hours in ITN9, and between five and eight hours in IAN007. The animal's breastbone was split and divided, followed by a lengthy and complex operation involving the removal of most of the native heart, a temporary heart and lung bypass, and implantation of the pig heart.

If the baboons recovered from the operation, they would be administered a similar immunosuppressive regime to that given during the other studies: a combination of [REDACTED] and [REDACTED] together with doses of highly toxic [REDACTED]

before and shortly after transplant. The second of these studies, IAN007, employed an additional immunosuppressant [REDACTED].

Study ITN9¹⁰⁴ killed ten baboons between March and September 1996. According to the study report, four animals died within a day of transplant, these fatalities being put down to technical failures. In fact, five of the animals – half of the group - died within 18 hours for technical reasons.¹⁰⁵ Two died because of fatal clotting complications arising from a size mismatch – the pig hearts were much bigger than the original baboons' hearts. The other three rapid deaths came after the grafts failed to beat properly.

In two of the remaining five animals, the doses of [REDACTED] led to serious side effects; the drug appears to be highly toxic to the bone marrow of baboons. **X215m** died of a pneumonia infection on day 4:

4	pm	Unsteady, weak, rapid and slightly harsh breathing, swollen around eyes, laboured breathing, lower abdominal region swollen. Occasionally adopts a sitting position, minimal activity.
	am	Quiet and huddled, liquid faeces
	pm	Quiet and huddled, laboured breathing, no response to stimuli, sitting on cage floor, swelling around eyes, oedema on lower abdomen, liquid faeces. Sacrificed for humane reasons.

While, **W213m**, the longest survivor, had to be killed on day 9 due to pancytopenia, the depletion of vital blood cells, which can be a consequence of bone marrow damage:

8	pm	Quiet but alert, huddled, swelling around wound and lower abdomen, liquid faeces contained some blood stained mucus, observed shivering.
	am	Quiet but alert, huddled, occasionally collapsed on cage floor, liquid faeces, vomit in tray.
9	pm	Quiet but alert, dose sites bruised but not bleeding, dark liquid faeces passed.
	am	Quiet but alert, body tremors, unsteady movement, dark brown liquid faeces, general bruising around body.
	pm	Sacrificed for humane reasons.

Acute vascular rejection (AVR) of the xenografts killed the remaining three animals on day 5. Two of them died before they could be euthanased:

W211m	pm	Quiet and sitting on bottom of cage. Vomit in cage, abdomen swollen. Found dead.
X221m	am	Quiet but alert, vomit on back shelf, loose/liquid faeces. Animal died during examination.

V687m was destroyed when he became weak and had difficulty breathing.

A document entitled “Programme for the use of the 9 remaining baboons at HLS under the authorities of PPL 80/848”¹⁰⁶ (estimated date: summer 1997) describes how

¹⁰⁴ See folder ITN19.

¹⁰⁵ Schmoekel et al. “Orthotopic heart transplantation in a transgenic pig-to-primate model”.

Transplantation, Vol. 65, 1570-1577. No.12 June 27, 1998.

¹⁰⁶ See File [REDACTED]

Imutran were looking to try out a new immunosuppressive regime – i.e. [REDACTED] - in orthotopic heart xenotransplantation. This proposal resulted in study IAN007, for which six rather than the nine specified animals were vivisected.

Although only one animal is said in the study report to have died as a result of a technical failure, another document – a surgery report submitted to the Home Office by Imutran in January 1998¹⁰⁷ – reveals another surgical failure. The first animal, **X210f**, died during surgery. Her new heart would not start beating – a post-mortem diagnosed HAR.¹⁰⁸ Imutran suggest that this may have arose from the primate having a particularly high level of anti-pig antibodies (known as APA), resulting in a very strong immediate immune reaction to the graft, despite the presence of hDAF on the heart.¹⁰⁹

One of the additional innovations in study IAN007 was that a tube was inserted and left in the chest of the transplanted animal for two hours following surgery. It was used to drain the chest of accumulated fluids and gas, which were monitored for evidence of bleeding or air leak,¹¹⁰ both of which would have signalled serious complications. However, after the tube was removed, **X239m**, was discovered to have a pneumothorax – air trapped in a lining of the lung called the pleural cavity – a condition that can lead to a collapsed lung. For the next two days the pneumothorax expanded, forcing Imutran to destroy the victim:

2	pm	Very subdued, heavy lidded, weak when moving, breathing rate appears to have increased, on return to cage after treatments, breathing heavily and audibly, initially no reaction to external stimuli, after approximately 15 minutes, became more aware of surroundings, breathing more settled.
	am	Vomiting. Very quiet but alert when disturbed, urine and faeces passed, appears swollen around the throat. Sacrificed for humane reasons.

X202f survived for 11 days before succumbing to another complication of surgery – a breast bone wound infection that would not respond to antibiotics. She seems to have been very ill for at least three days before being destroyed:

8	pm	Quiet and huddled, eyes partially closed, periodic severe tremors in upper torso and head, later animal appears more comfortable.
---	----	---

But the wound degenerated:

9	pm	Quiet but alert, reluctant to move, breathing appears normal. Loose faeces. Wound slightly open between nipples, cloudy yellow/white discharge seeping from wound.
10	am	Quiet but alert, eyes closed. Loose faeces.
	pm	Loose faeces.
11	am	Quiet but alert, split in middle of wound, animal unsteady. Loose faeces. Animal sacrificed for humane reasons.

¹⁰⁷ See Files WCB30.1→WCB30.3.

¹⁰⁸ See File [REDACTED]

¹⁰⁹ See File [REDACTED]

¹¹⁰ [REDACTED] "Life Supporting Function for Over One Month of a Transgenic Porcine Heart in a Baboon." *Journal of Heart and Lung Transplantation*. Vol. 19, No. 12.(2000): 225. Also see file [REDACTED]

The cause of death of **X234f** after 12 days was attributed to “sudden cardiovascular decompensation”. She “exhibited a sudden and rapid decline leading to collapse virtually immediately after oral gavage.” Imutran scientists appear to have been unsure of the precise cause of this fatality, but they surmise it may have resulted from a chain of events that unfolded like this: an impaired heartbeat (‘dysrhythmia’) caused a rapid build up of fluid in the lungs (‘flash pulmonary oedema’) and simultaneous abnormality of the nervous control of the circulation and heartbeat (‘vaso-vagal event’). This, in turn, triggered a dramatic drop in blood pressure (‘profound hypotension’). Combined with a possibly subnormal (though not, on its own, immediately life-threatening) heart function, the effect was lethal:

12	am	Quiet but alert, occasionally active. Dark faeces.
	pm	Animal quiet and deteriorating rapidly. Sacrificed for humane reasons.

A similar cause of death was surmised for the longest survivor in the group: **X201m**. Appendix 9 of the study report notes that X201m’s transplant had almost tripled in weight between transplant and post-mortem. Nevertheless, he clung to life for 39 days and his single case was written up by Imutran scientists and published in the *Journal of Heart and Lung Transplantation* in February 2000.¹¹¹ Imutran were keen to highlight his case because he had earned the dubious distinction of achieving “the longest survival recorded to date of a discordant orthotopic cardiac xenograft.” In this paper, Imutran claim that:

“Throughout the first 38 post-transplant days the baboon was active and energetic, moving freely about his enclosure, displaying interest in food and interacting socially with a pairing partner.” (226)

This is an implausibly upbeat interpretation of his condition given what was recorded in his clinical signs record.¹¹² Although this record declares him to have been “alert and active” on several mornings and afternoons, this was certainly not the case “throughout” his last 39 days:

1	am	Alert, aware of surroundings, slightly unsteady, urine passed.
	pm	Slow moving but aware of surroundings. Dark loose faeces.
2	am	Sitting on perch, constantly resting head, very slow movements. Loose faeces.
	pm	Quiet but alert, sitting on perch.
13	am	Alert and occasionally active, vocalising.
	pm	Quiet, sitting in cage corner on shelf, appears to be trying to sleep.
14	am	Alert and occasionally active, vocalising.
	pm	Quiet but alert, occasionally active.
15	am	Quiet and huddled, reluctant to move, some abdominal breathing seen, slightly unsteady.
	pm	Quiet but alert, sitting on wooden base.
16	am	Quiet and huddled, reluctant to move.
20	am	Alert and active. Normal faeces.
	pm	Quiet but alert at times.
21	am	Alert, not very active, sitting on perch.
	pm	Quiet and huddled, alert if stimulated. Slow movements, slight abdominal

¹¹¹ [REDACTED] “Life Supporting Function for Over One Month of a Transgenic Porcine Heart in a Baboon.” *Journal of Heart and Lung Transplantation*. Vol. 19, No. 12.(2000): 224-229.

¹¹² See clinical signs for IAN007, pp.61-64 to compare.

22	am pm	breathing. Alert, not very active, sitting on perch. Quiet but alert, sitting on perch.
26	am	Alert and fairly active, sitting on perch
	pm	Quiet, sitting on perch, reluctant to move/some movement.
27	am	Quiet but alert, sitting on perch, fairly active. Dark faeces.
	pm	Alert and active, vomiting. Wound appears okay.

Until his final deterioration for the last six days:

34	am	Quiet but alert, sitting on perch, aggressive and active when stimulated. Dark faeces.
	pm	Quiet but alert, unresponsive to stimulation, sitting on cage floor. Normal faeces.
35	am	Sitting on perch, huddled but not asleep.
	pm	Quiet and huddled on perch.
36	am	Sitting on perch, huddled but not asleep, alert when approached.
	pm	Biopsy performed under anaesthetic.
37	am	Huddled, sitting on ledge, reluctant to move.
	pm	Quiet and huddled, alert when stimulated. Dark faeces.
38	am	Alert but no movement, moves when stimulated. Normal faeces.
	pm	Quiet but alert when approached.
39	am	Asleep in corner of cage, reluctant to move when stimulated. Dark faeces.
	pm	Very subdued, reluctant to move even when stimulated. Died following collapse.

The remaining baboons used in IAN007 was a female, **X206f**. She survived 22 days, until:

21/22	o/n	Continuously lying down, noisy laboured respiration, extreme difficulty breathing, vocalising. Died prior to sacrifice (01.17 am).
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According to the Imutran report on the study, she “was dosed with [REDACTED] via oral gavage and several minutes later developed progressive dyspnoea [breathing difficulties], weakness and, eventually, became unresponsive.”¹¹³ Her cause of death is listed later as “Acute cardiopulmonary failure.” Curiously, a surgery report for March 1998, submitted to Home Office Inspector [REDACTED], claims she was **euthanased** following a “myocardial infarction”, or heart attack.¹¹⁴

Earlier, in section 3.3, we referred to the apparent vivisection of seven baboons carrying Simian Herpes B Virus, which seems to have been contemporaneous with study IAN007. The other significant aspect of these procedures was that they appear to have been carried out without a crucial pre-surgery blood sample being taken. We deduce that the sample in question was supposed to measure the level of anti-pig antibodies in the baboons’ blood. This would be very important because it was thought that the levels of these antibodies would influence the subsequent rejection processes that the porcine organ would experience, including whether it was hyperacutely rejected despite the presence of hDAF on the graft.¹¹⁵ Furthermore, fluctuations in these antibody levels after xenotransplantation were used to help

¹¹³ See File [REDACTED]

¹¹⁴ See File WCB31.1 & WCB31.2.

¹¹⁵ See Files [REDACTED] & [REDACTED]

diagnose episodes of rejection.¹¹⁶ Without a baseline reading, these fluctuations would be harder to interpret. Hence the exasperated comment on the relevant document that appears to have been written by [REDACTED]: “[REDACTED] I can not believe we did 7 transplants without pre-transplant antibodies.”¹¹⁷

4.4 Summary of chapter

This chapter set out to describe the fate of the wild-caught baboons subjected to xenotransplantation research. We find the evidence contained in the clinical signs appendices to each study report deeply disturbing. The reason for recounting the suffering and death of these animals is to ensure that it does not go unacknowledged. For there is an urgent moral imperative to absorb the implications of the ordeal of the baboons.

In particular, the following question arises:

- Can the infliction of such pain and death on other animals, not least non-human primates, ever be justified?

Alternatively, this question arises for those who, like the Government, believe the pain infliction and killing are justified if the ‘benefits’ are likely to outweigh the pain:

- Do the benefits that have been produced, or could reasonably have been expected to arise, justify these terrible costs?

This chapter concentrates on the ‘costs’ side of the equation, though some issues have an important bearing on the ‘benefits’ aspect.

The baboons were subjected to severe surgical procedures and immunosuppressive drug regimens as Imutran sought to investigate ways of enabling primates to accept transgenic hearts from pigs. Six baboons had piglet hearts grafted on to their necks. Twenty-seven had piglet hearts inserted into their abdominal cavity. Sixteen baboons’ hearts were replaced with piglet hearts.

Legal ‘severity limits’ are supposed to be attached to animal experiments. The scale of the suffering inflicted on animals such as W205m during Study ITN6 provokes pressing questions about whether these procedures exceeded the severity limits placed on them, or, if they did not, the effectiveness of the regulation of these experiments that are supposed to prevent the licensing of “procedures likely to cause severe pain or distress that cannot be alleviated.”

Of these 49 animals, 15 (31%) appear to have died within 24 hours simply because of ‘technical failures’ – complications with surgery. Some of these deaths are attributed to apparently avoidable failings, such as a size mismatch between the pig heart and the monkey’s body or the source piglet being too young. Two more animals are listed as succumbing to hyperacute rejection (HAR), despite the grafted organ having been

¹¹⁶ See File [REDACTED]

¹¹⁷ See File WCB22.1.

genetically manipulated in an effort to evade this rapid and totally destructive rejection process. One of the studies was a 'control' study that used non-transgenic organs. These baboons were effectively condemned to certain death within a few days.

The remaining animals died as a result of one of the following:

- Infections, often arising from surgical wounds in the context of drastically impaired immune systems.
- Other toxic effects of the immunosuppressive drugs.
- Heart failure as a result of rejection.
- Heart failure for apparently inexplicable reasons.

In published papers, Imutran refer to their two longest survivors. One monkey received a pig heart into her abdomen, while her own heart was left in place. Imutran scientists claim that for her and other recipients they had "developed an immunosuppressive strategy... that allows prolonged xenograft survival while being **well tolerated** by recipients." (my emphasis) We find this statement somewhat implausible, in the light of the recorded clinical signs.

The other 'extended' survival occurred in an orthotopic transplant study, where the baboon's heart is replaced with the pig's. One animal lived for 39 days. In this instance, Imutran claim:

"Throughout the first 38 post-transplant days the baboon was active and energetic, moving freely about his enclosure, displaying interest in food and interacting socially with a pairing partner."

Once again, the clinical signs paint another, more wretched picture.

In a surgery report to the Home Office Inspector, Imutran state that one baboon, X206f, was euthanased after she had suffered a heart attack. However, the clinical signs record says she "died prior to sacrifice." This discrepancy raises concerns about the accuracy and completeness of information supplied by Imutran to regulatory authorities. The scrutiny of such information should form part of an enquiry into the entire affair.

Although Imutran predicted that they would be ready for clinical trials of transgenic pig hearts by the end of 1996, in the summer of 2000 the goal of achieving consistent extended survival of transgenic pig hearts in primates without provoking severe toxic side-effects remains as elusive as ever. The biological barriers to such a radical and unnatural procedure have been predictably inscrutable and unyielding.

The points outlined above should be set against Home Office claims regarding how it regulates the operation of the 1986 Act. In conducting the cost-benefit assessment, the Chief Inspector states that the following issues are taken into account:

- Judgement on the likely severity of the adverse effects on animals;
- Standards of care and accommodation;
- Technical competence of the people and establishments to be involved in the project;
- Relevance of the animal “model” to human condition;
- Likelihood of “success”;
- Soundness of experimental design;
- How the data generated will be used;
- Utility of the product or substance being tested

Part V will discuss in more detail the issue of what benefits and/or disbenefits are likely to arise from xenotransplantation, and thus the legal and ethical validity of incarcerating and killing baboons, cynomolgus monkeys and the pigs themselves in order to develop and supply xenografts.

In the meantime, we should reflect upon the intense and protracted suffering of the wild-caught baboons used by Imutran at HLS over the last four to five years – a programme conducted with the blessing and support of the Home Office.

Index of filed documents accompanying PART II: WILD-CAUGHT BABOONS IN XENOTRANSPLANTATION RESEARCH

WCB1.1: Letter from [REDACTED] (Home Office) to [REDACTED] (Imutran), 21 February 1997: “Animals (Scientific Procedures) Act 1986 – Overseas source of baboons.”

WCB2.1: [REDACTED]

WCB3.1 & WCB3.2: “Application from a Project Licence Holder or Deputy for Permission to Acquire Non-Human Primates from a Non-Designated Breeding Centre for use in Regulated Procedures.” Submitted 23.6.98. Approved 29.7.98.

WCB4.1: [REDACTED]
[REDACTED]

WCB5.1: [REDACTED]
[REDACTED]

WCB6.1: [REDACTED]

WCB7.1: [REDACTED]

WCB8.1: [REDACTED]

WCB9.1: [REDACTED]
[REDACTED]

WCB10.1: [REDACTED]
[REDACTED]

WCB11.1: [REDACTED]

WCB12.1: [REDACTED]

WCB13.1: [REDACTED]

WCB14.1: Fax from [REDACTED] to [REDACTED] (Imutran), 15.4.99.

WCB15.1: [REDACTED]

WCB16.1: [REDACTED]

WCB17.1 & WCB17.2: [REDACTED]
[REDACTED]

WCB18.1: Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspector), 10 February 1999.

WCB19.1 & WCB19.2: Discussion document. "Cape Town possibilities for expanding Imutran XenoTx." [REDACTED]/10/98.

WCB20.1→WCB20.12: Fax from [REDACTED] to [REDACTED] BABOON BREEDING PROJECT", 31 May 1999.

WCB21.1→WCB21.3: Letter from [REDACTED] (Ministry of Agriculture, Fisheries and Food) to [REDACTED] (Imutran: [REDACTED]), "IMPORT OF BABOONS INTO [REDACTED]", 8 February 1999.

WCB22.1: Imutran Document, "Pre-surgery Anti-pig Antibody titres in baboons", [REDACTED] 06/03/98.

WCB23.1→WCB23.13: [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

WCB24.1→WCB24.7: "Home Office Six Monthly Report. July-December 1999. Imutran."

WCB25.1→WCB25.30: [REDACTED]
[REDACTED]
[REDACTED]"

WCB26.1→WCB26.3: Fax from [REDACTED] (HLS) to [REDACTED] (Imutran), shortly after Wednesday 23 June 1999, "Xenotransplantation Programme at Huntingdon Life Sciences."

WCB27.1→WCB27.3: [REDACTED]

WCB28.1→WCB28.3: [REDACTED]
[REDACTED]
[REDACTED]

WCB29.1: Document/Table: "Use of Baboons in Comparative IS Study." Estimated date: mid-May 1997.

WCB30.1→WCB30.3: Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspector), 13 January 1998, including surgery reports for November and December 1997.

WCB31.1 & WCB31.2. Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspector), 20 April 1998, including surgery report for March 1998.

WCB32.1: [REDACTED]
[REDACTED]
[REDACTED]

WCB33.1: [REDACTED]

WCB34.1: [REDACTED]
[REDACTED]

PART III

CYNOMOLGUS MONKEYS IN XENOTRANSPLANTATION RESEARCH

CHAPTER 5

The importation of cynomolgus monkeys

5.1 Importations

From the study reports, it can be ascertained that 189 cynomolgus monkeys originated from a breeding company [REDACTED] in Mauritius, 181 from the [REDACTED] Philippines, and one from Indonesia. The reason that these figures do not give a sum total of 424 – the number of cynomolgus monkeys used in experiments according to the study reports – is that the precise origin of the animals is not always specified in the study reports, particularly for studies not involving transplantation procedures. Until the latter half of 1996, monkeys used in experiments originated from Mauritius. From this point onwards, [REDACTED] the Philippines became the source.

At least 117 of the animals came through the former monkey supply business [REDACTED] [REDACTED] closed earlier this year following protests against their trade. More recently, shipments of animals have been organised by [REDACTED] ¹¹⁸ run by [REDACTED] (many documents show that he has also traded under the name [REDACTED]). Having selected suitable animals by screening them for infectious agents such as the dangerous Simian Herpes B virus, Imutran left the bulk of the work of organising the shipments to Huntingdon Life Sciences (HLS).

Three “Primate Acquisition” forms reveal:

1. the procurement of 15 cynomolgus monkeys from Mauritius on 9 July 1996 for bone grafts to be performed upon them¹¹⁹;
2. the following day, Imutran’s [REDACTED] requested the acquisition of 22 monkeys from the Philippines for use in kidney transplant experiments;¹²⁰
3. on 14 October 1996, Imutran’s [REDACTED] approved the acquisition of a further ten monkeys from the Philippines to test pig kidneys.¹²¹

Each of the animals cost £2,150.

A fax from [REDACTED] to [REDACTED] at HLS, dated 23 February 1998, refers to Home Office permission to import 40 “cynos” from [REDACTED] to HLS’s facility at [REDACTED]. Imutran had selected a list of animals following screening for

¹¹⁸ [REDACTED]

¹¹⁹ See Files [REDACTED] & [REDACTED]

¹²⁰ See File [REDACTED]

¹²¹ See File [REDACTED]

infectious organisms. [REDACTED] is mentioned, though [REDACTED] says: “from this stage I will leave the organisation of the import to you guys.”¹²²

Another paper discloses that 36 cynomolgus monkeys were due to arrive at [REDACTED] on 21st October 1997.¹²³ It also explains why the monkeys went straight to [REDACTED] rather than Huntingdon upon arrival in the UK: “They will be kept in quarantine here for 4-6 weeks before being transported to HLS for a minimum of 2 weeks acclimatisation.”

Later in 1998, on 6th November, [REDACTED] informed Home Office Inspector [REDACTED] that “Imutran have placed a reserve on 100 cynomolgus monkeys at [REDACTED] for use during 1999.”¹²⁴ Subsequently, 35 animals – aged between 35 and 41 months¹²⁵ – were transported to HLS at the end of March 1999¹²⁶, while an application was submitted to the Home Office on 10 May 1999 to import a further 40 monkeys in the third quarter of the year.¹²⁷

5.2 Deaths in transit

Transportation half way across the globe is a potentially lethal ordeal for primates. According to Home Office Minister Mike O’Brien, eight cynomolgus monkeys have died during transit to the UK since 1995, one from Israel, three from Mauritius and four from the Philippines. Attributed causes of death included “enteritis” (inflammation of the small intestine, usually leading to diarrhoea), “shigellosis” (bacterial infestation causing dysentery) and “a trauma to the head.”¹²⁸ (The Oxford Concise Medical Dictionary defines a trauma as “a physical wound or injury, such as a fracture or a blow”). Three of the monkeys were found dead on arrival in Paris from the Philippines in one consignment in 1998.

O’Brien said in his answer to a question tabled by Norman Baker MP about specific dates of deaths of animals imported for the purpose of xenotransplantation research: “we cannot... confirm whether all of the [dead] animals listed above were to be used for this [i.e. xenotransplantation] purpose.” The point however was not whether all of the monkeys were imported for this purpose, but rather which, if any, were. In fact, a set of documents reveals that the three monkeys who died on their way from the Philippines in 1998 were indeed destined for xenotransplantation research, and the Home Office were and are fully aware of this.

The three animals were found dead in Paris on the morning of 5 August 1998, some 35 hours after being packed into crates at [REDACTED] site in the Philippines. After a two and a half hour journey from [REDACTED] to Manila airport by truck, the animals were held in [REDACTED] Warehouse before departing nine hours after arriving at the airport. The flight took some 17 hours, arriving in Paris just before

¹²² See File [REDACTED]

¹²³ See File HLSAPP5A.3

¹²⁴ See File [REDACTED]

¹²⁵ See File [REDACTED]

¹²⁶ See Files [REDACTED] & [REDACTED]

¹²⁷ See File CY10.

¹²⁸ Written Answers, Hansard, 28 June 2000, Column 522W & 521W.

six o'clock on the morning of the 5th. At 10:50am the animals were found dead. They were left in their crates while the whole consignment of 33 travelled onwards to HLS' research centre at [REDACTED] by truck and ferry through Dover. The monkeys eventually arrived at [REDACTED] just after midnight on the morning of the 6th August, a total journey time of 48 hours according to [REDACTED], Imutran's [REDACTED] (though I calculate a total journey time of 50 and a half hours).¹²⁹

The Home Office was fully aware that these animals were intended for use in xenotransplantation experiments. An application to import the animals would have been made to the Home Office by Imutran, referring to a project licence number that authorises xenotransplantation research, and the stated purpose on the form would have given the reason why Imutran wanted to use cynomolgus monkeys in their experiments. HLS staff immediately informed the Home Office about the deaths of the animals when they were found, and Imutran liaised with the Home Office in the aftermath of the deaths.

The review of this incident reveals a number of disturbing factors. These fall roughly into four categories: the size of the crates, ventilation, females in heat, and the journey time. Home Office Minister Mike O'Brien stated that the deaths "were probably due to a combination of factors,"¹³⁰ while a MAFF expert says:

"My experience is that deaths often happen when several factors, each of which could be problematic, combine to cause circumstances too severe for the animal to tolerate."¹³¹

Crate size

"The internal dimensions of the crates was; Depth 39cms, width 24cms and height 44cms."¹³² This was so small that "the containers were not large enough to allow these particular animals to stand up and turn around freely."¹³³ According to MAFF's Livestock Transport Advisor, [REDACTED], "The reports from the consignor/shipper and consignee recognise that the dead animals were probably too large (because they were larger animals than normally shipped) for their containers."¹³⁴ International Air Transport Authority (IATA) regulations state that transit crates should "allow the animal to stand, turn and lie down in a natural manner."¹³⁵

The idea of not being able to stand up and turn around properly for two whole days hardly bears thinking about. Besides any role this may have played in killing the three monkeys, the welfare impact on the other thirty higher primates must have been severe.

¹²⁹ See Files CY5.1 & CY5.2.

¹³⁰ Mike O'Brien MP, Written Answers, Hansard, 28 June 2000, Column 522W & 521W.

¹³¹ See File CY5.6.

¹³² See File CY5.3.

¹³³ Mike O'Brien MP, Written Answers, Hansard, 28 June 2000, Column 522W & 521W.

¹³⁴ See File CY5.5.

¹³⁵ See File CY5.3.

One of the most interesting aspects of this affair is the comparison between the version of events related in the hitherto-secret documents compared to that given by Mr O'Brien in his Written Answer on 28 June 2000: in particular, the Home Office Minister's omission of the regulatory breaches that occurred during this fatal journey and the protection he gives to xenotransplantation research.

With regard to regulations concerning the dimensions of the crates, O'Brien states: "International Air Transport Association minimum dimensions were not breached". However, as MAFF's [REDACTED] observes with regard to IATA regulations: "the over-riding rule is that dimensions must relate to the size of the animal."¹³⁶

Ventilation

The post-mortem reports could not identify a definitive cause of death, though bleeding from the nostrils was found to be a common feature. [REDACTED] suggests that if the nose-bleeding was associated with a lack of ventilation then the fact that the dead monkeys were in 'middle compartments' with fewer airholes is likely to be significant. O'Brien acknowledges this as a possible contributory factor in the deaths of the animals:

"all the dead animals had been in central compartments, which were less well ventilated."

The phrase "less well ventilated" does not quite convey the reality of ventilation inadequate to the point of potentially contributing to the deaths of three monkeys. Neither does it reflect the fact that containers were in clear breach of IATA regulations. For the compartments were only ventilated on two sides, in breach of the IATA regulation that specifies that containers must be "ventilated on at least three sides."¹³⁷

Females in heat

[REDACTED] also highlights IATA regulations that advice against shipping females in heat because of the adverse reaction it has on males in the shipment. He notes that many of the females exhibited "sexual swelling" and wonders whether this indicates that they were in heat, which in turn might have exacerbated the stress of the male monkeys to the point of death. This issue is not dealt with by Mike O'Brien.

Journey time

Given the cramped conditions and inadequate ventilation, the journey time of 48 hours must have been a terrible ordeal for the animals. Ironically, O'Brien implies in his written answer that many airlines refuse to fly animals to the UK because of

¹³⁶ See File CY5.5.

¹³⁷ See File CY5.5.

“harassment from animal rights activists” and that this in turn results in longer journey times which may have contributed to the deaths of animals.

Mr O’Brien did not reveal the journey time in his Parliamentary answer. We cannot be sure whether the journey time of at least **48 hours** accorded with that stated by Imutran on their application to the Home Office to acquire this batch of monkeys. However, two other applications for identical importation procedures both give an Expected Duration of Journey of only **30 hours**.¹³⁸ This raises concerns that, as in the case of the May 1999 consignment of wild-caught baboons,¹³⁹ the actual journey time may not have been in accordance with the details supplied on the application form, and thus it may have rendered the importation unauthorised.

If this is indeed the case, then one wonders what sanctions the Home Office can and does implement in such instances. There is, however, no evidence to suggest that the Home Office is sufficiently concerned about such apparent breaches of acquisition licences. Without punishment for breaches, the regulations are a sham, with the Home Office merely going through the motions of regulation rather than enforcing them. This impression is reinforced by other aspects of the Home Office’s response to the deaths of the three primates.

Following these deaths, the Home Office ‘suspended’ [REDACTED] from its list of “approved suppliers” while it asked the Ministry for Agriculture, Fisheries and Food (MAFF) for advice about the cause of the deaths. However, this suspension appears to have had little teeth as in early December, during the period of suspension, HLS were receiving another shipment of cynomolgus monkeys from [REDACTED]. [REDACTED] tells his colleagues at Imutran that “provided the crates are satisfactory and the shipment is problem free then [REDACTED] will be re-instated to the Approved Suppliers listing”¹⁴⁰ by the Home Office. It seems as if the Home Office’s ‘suspension’ affected the procedural paperwork relating to the licensing of imports from [REDACTED] rather than importations themselves: a rather attenuated form of suspension that could hardly be said to give serious consideration to the safety and welfare of the animals.

Nonetheless, the suspension of [REDACTED] from the approved suppliers list was “of great concern to” Imutran because the company had reserved 100 cynomolgus monkeys at [REDACTED] for importation during 1999, though an application to the Home Office for each shipment had not been submitted. [REDACTED] wrote to [REDACTED] on 6th November 1998 regarding [REDACTED]’s suspension, saying that in the light of Imutran’s reservation of 100 monkeys: “...I would be very grateful if you could give me some indication of when the situation will be resolved.” Less than two weeks later, [REDACTED] tells [REDACTED] at HLS that he telephoned [REDACTED] on 18th November and “explained that I was intending to import a group of 30 cyno’s in January next year and asked him the situation regarding the approval of [REDACTED] as a supplier, again he felt this issue would be resolved soon.” [REDACTED] continues: “In short I am to contact him again late next week when he feels (confidently!) that he will be able to give me definitive answers...”¹⁴¹

¹³⁸ See Files in CY8 & CY10.

¹³⁹ See section 3.1.

¹⁴⁰ See File CY5.16.

¹⁴¹ See Files in CY7.

Come January 1999, and [REDACTED] had still not been re-instated as an approved supplier. This did not put off Imutran from making an application to the Home Office on 22nd January to import forty monkeys from [REDACTED] during the first quarter of the year.¹⁴² Less than three weeks later, [REDACTED] wrote to [REDACTED] again, explaining:

“Preparations for the importation of a group of up to forty *Cynomolgus* macaques are well advanced, I expect to be in receipt of the pre-importation health screen results by the end of this week. I understand that the situation regarding the status of [REDACTED] as an approved supplier should be resolved shortly. I would therefore appreciate it if you could approve my earlier request for authority to import these animals as soon as possible.”¹⁴³

The shipment of monkeys arrived into the UK at the end of March.

In answer to the section of Norman Baker MP’s Parliamentary Question that enquired about the Home Office’s response to the deaths of primates, according to Mike O’Brien MP, the containers had “been enlarged and redesigned to rectify” the problems that killed the three *cynomolgus* macaques. While any actions undertaken to mitigate the suffering of animals are to be welcomed, this hardly seems like an adequate response to the deaths of three higher primates during transport to the UK in crates that broke at least two fundamental regulations and may have taken 18 hours longer than the time approved for the acquisition. Why have no sanctions been applied to the individuals and organisations responsible for this importation? What strength do regulations have if their transgression – to deadly effect – fails to attract censure or punishment?

The final intriguing aspect of this incident is to be found at the end of a letter from [REDACTED] to his colleagues at Imutran, [REDACTED], [REDACTED] and [REDACTED]. He says:

“As far as we are concerned I believe this to be the last we should hear on this matter, please note that throughout this investigation I have orchestrated it such that Imutran are entirely anonymous.”¹⁴⁴

Why were Imutran so concerned about anonymity? Was this in relation to MAFF rather than the Home Office, given that the Home Office were fully aware of the incident (or at least the Home Office Inspector, [REDACTED] was)? Were the Animal Procedures Committee (APC) informed about the name of the importing organisation?¹⁴⁵ In any case, the desire for anonymity reflects the seriousness of the incident, which in turn makes the Home Office’s feeble response all the more abysmal.

¹⁴² See Files in CY8.

¹⁴³ See File WCB18.1.

¹⁴⁴ See File CY5.16.

¹⁴⁵ See Animal Procedures Committee – Minutes of Meeting February 1999, Section 9. <http://www.apc.gov.uk/reference/feb99.htm>. These minutes do not mention that the crates actually broke two critical regulations: were the APC informed about the breaches by the Home Office Inspectorate upon whom they depend for detailed information about such matters?

CHAPTER 6

Research on cynomolgus monkeys

At least 424 cynomolgus monkeys (*Macaca fascicularis*, or also known as *crab-eating macaques*) were used and killed in the xenotransplantation research commissioned by Imutran at contract laboratory Huntingdon Life Sciences (HLS). However, study reports and a table of studies indicate that up to eight further studies¹⁴⁶ may have taken place for which final draft study reports have not become available,¹⁴⁷ so the true figure is likely to be closer to 600 macaques.

If they survived the ordeal of importation to HLS from Mauritius, Indonesia or the Philippines, the monkeys were used in a wide range of experiments:

- In one “developmental” study for which no final report is available, ITN1, cynomolgus monkeys were cut open and killed to transplant their hearts into the necks of baboons. We suspect that at least eighty monkeys died for this study.¹⁴⁸
- Three heterotopic cardiac xenotransplantation studies took place between late 1994 and January 1996 involving the grafting of piglet hearts into the abdomens of the monkeys: ITN2, ITN3 and ITN7. At least 67 monkeys died in these studies – the true figure may be greater than 100 because no study report is available for ITN2, and the figure of 67 is derived from the other two studies alone.
- One study, ITN5, saw pancreatic islet cells from pigs implanted close to the kidneys of 37 monkeys.
- In 1996 and 1997, thirty monkeys were sacrificed in two studies (ITN8 and ITN15) that transplanted bone from pigs into the tails of the monkeys. A further study, ITN10, accounted for 12 monkeys who were killed to test the grafting of cartilage from pigs into the animals’ knees.
- A further eight studies were conducted on cynomolgus monkeys which did not involve transplantation procedures, but instead aimed to test various immunosuppressive treatments for toxicity and effectiveness. These studies took place sporadically between September 1996 and February 1999, using 59 primates.
- The majority of the experiments that cynomolgus monkeys were subjected to involved the heterotopic transplantation of porcine kidneys into their abdomens. Upwards of 211 macaques died in these studies that stretched from

¹⁴⁶ Studies ITN1 (transplantation of hearts from cynomolgus monkeys into the necks of baboons), ITN2 (heterotopic abdominal cardiac xenotransplantation), and IAN011, IAN012, IAN023, IAN025 AND IAN027 (all heterotopic renal (kidney) xenotransplantation studies)

¹⁴⁷ See Files in [REDACTED]

¹⁴⁸ See beginning of chapter 4.

July 1995 through to at least June 1999. In addition to the 19 reported studies, at least four further similar studies took place for which final draft reports have not become available, and we guess that such studies were taking place as recently as February 2000.¹⁴⁹

To a large extent the ordeal endured by these animals, and the ethical and legal concerns raised by their experiences – echo the points to have emerged from the analysis of the vivisection of baboons in Chapter 4. We shall leave the discussion of the studies involving the grafting of porcine kidneys into the monkeys – the main thrust of Imutran’s research – until the final section of this chapter. In the meantime, we will examine the other experiments conducted on cynomolgus monkeys by Imutran at HLS.

6.1 Heterotopic cardiac xenotransplantation

Three of Imutran’s earliest studies, ITN2, ITN3 and ITN 7 involved the transplantation of piglet hearts into the abdomens of cynomolgus monkeys.

ITN2, in common with ITN1, was considered a “developmental” study and, therefore, no final report was required, although data for the study should have been archived at HLS and/or Imutran.¹⁵⁰ From published papers, this study would seem to have included the transplantation of transgenic and non-transgenic pig organs without the use of immunosuppressant drugs: the animals survived just a few days on average.¹⁵¹

ITN3 – “Heterotopic cardiac xenograft transplantation in cynomolgus monkeys (Long term survival : Experiment 1) - took place between March 1995 and January 1996. It was the most expensive study that has come to this author’s notice, in terms of primates’ lives, killing 61 animals. The surgical procedure was similar to that performed upon baboons in heterotopic abdominal cardiac xenotransplantation. Thus the transplanted pig hearts were not life-supporting. Four of the monkeys also received transplants of foetal pig islets either beneath the membrane (capsule) that surrounds the kidney or in a pocket fashioned in the lining of the abdomen (the greater omentum) during the procedure.

An apparently related paper entitled, “Operating Protocol for Heterotopic Abdominal Heart Transplantation – Pig to Cynomolgus Monkey”¹⁵², written by [REDACTED], one of Imutran’s surgeons, also describes the surgical procedure to be performed on the source and recipient animals. In most respects, this procedure is similar to that described in the study report. There are, however, two additional details that merit attention because of their potential implications for animal welfare and the cost-benefit assessment.

¹⁴⁹ See Files [REDACTED]

¹⁵⁰ See Files HLSAPP1.4 and HLSAPP2.5.

¹⁵¹ “Xenogeneic transplantation”, *British Medical Bulletin* 1997; 53 (No.4): 904-920.

¹⁵² See Files in [REDACTED]

Firstly, [REDACTED] protocol states that once the pig's breastbone has been split open and the internal organs exposed:

"The heart size and morphology is inspected at this stage and if function and morphology is not suitable the procedure should be abandoned."

In effect, this would result in the waste of a pig's life. We regard such treatment of pigs as intrinsically wrong. However, even from a perspective that sanctions such treatment on the dubious grounds that the benefit to humans would outweigh the costs to the animals (i.e. the cost-benefit assessment that underlies current legislation on animal experiments), any wastefulness would appear to render such procedures illegitimate because of the lack of benefit accruing from the killing of the pig. This waste of lives is an issue that concerned the Government's advisory Animal Procedures Committee (APC), and will be scrutinised in more detail in chapter 8.

The second significant detail to emerge from [REDACTED] protocol concerns the surgery on the monkey recipient. [REDACTED] states:

"Occasionally as the animal recovers and tenses it's abdominal muscles the donor heart position and function may be compromised such that it becomes bradycardic [beating slows down] and may stop. If this bradycardia is detected early the abdomen can be reopened and the donor heart may be repositioned."

The possible repetition of anaesthesia and re-opening of the wound raises deep worries about the intensification of the suffering experienced by the cynomolgus monkey recipients.

In the event, out of 61 animals transplanted a staggering 33 died within 24 hours as a result of "technical failures." 24 of these monkeys "died or were killed whilst under general anaesthesia or during the immediate post-operative recovery phase in theatre... The remaining animals were sacrificed following their return to the animal unit."¹⁵³

The 28 survivors were returned to their cages and administered an immunosuppressive cocktail of [REDACTED]. They lived for an average of 25 days before being killed due to either xenograft failure, opportunistic infection arising from the immunosuppression, or drug toxicity. This was clearly a deeply disappointing outcome: an Imutran protocol drawn up by [REDACTED] for a range of studies, including this one, was based upon the assumption that 50% of the animals would survive 100 days.¹⁵⁴ Additionally, a fax from Sandoz Pharma, the multinational drug company who were supporting Imutran's research at the time, reveals that they were supplying drugs to Imutran during the period of this study based on the assumption of "3 month survival".¹⁵⁵

The animals are often noted to be either "quiet but alert" or "alert and active." However, other clinical signs recorded included:

¹⁵³ See File [REDACTED]

¹⁵⁴ See File [REDACTED]

¹⁵⁵ See File [REDACTED]

- Dark, loose and/or liquid faeces.
- Huddled.
- Unsteadiness.
- Little movement, reluctant to move or very slow movement.
- Eyes and muzzle puffy.
- Sneezing.
- Salivation.
- Prepuce (foreskin) swollen.
- Blood-stained mucus in loose pale faeces.
- Swelling around eyes.
- No reaction to stimulation.
- Blood in tray.
- Piloerection (hair standing on end)
- Oedema (fluid-filled swelling) in abdomen.
- Reluctant to use legs.

Monkey W468f's tail was amputated due to the spread of gangrene towards her body. She also suffered from congested breathing. Two animals, W741m and W264f were found dead on day 2. The young male monkey had been observed huddled on the cage floor the previous day. W747m was found dead on the afternoon of day 22: "Rigor mortis set in."

On eleven occasions, the study report states: "No comment made on condition of animal". "Records not available" appears in 14 instances. In a subsequent report, Imutran claimed that there was a "fundamental shortfall in Good Laboratory Practice compliance" for this study and others around this time.¹⁵⁶

In a letter to [REDACTED], Imutran surgeon [REDACTED] observes that a major cause of the primate deaths is "general debility and non-specific diarrhoea." [REDACTED] deduces that the monkeys lose weight and become weak "due to nausea secondary to the immunosuppressive agents."¹⁵⁷ A published paper admits that "five animals... had to be euthanased due to gastrointestinal toxicity, resulting in severe diarrhoea," a

¹⁵⁶ See section 7.3 and files in HLSAPP2.

¹⁵⁷ See File HLSAPP5B.2.

result of drug toxicity.¹⁵⁸ Two other animals' grafted organs are said to have been rejected. However, the papers that invoke this experiment refer only to ten out of the 28 surviving monkeys.¹⁵⁹

Study ITN7, optimistically subtitled "Long term survival : Experiment 2", was similar to ITN3 except for the intention to administer an additional immunosuppressant, [REDACTED]. However, all four monkeys transplanted in January 1996 died within 24 hours of the procedure, leading to the study being aborted. Significantly, the clinical signs for one animal, W26f, suggest "rejection" as a possible cause of immediate graft failure. If this were true, it would hint strongly at the presence of hyperacute rejection, the process supposedly abolished by the transplant of organs from Imutran's genetically manipulated pigs. In turn, if hyperacute rejection was confirmed as the cause of this graft failure, it would raise further serious questions about the reliability of this technology.

Given the disastrous outcome of this study and the 54% failure rate in ITN3, it is hard to understand how the Home Office came to issue a project licence to perform these procedures. The Home Office, after all, is supposed to be guided by the "Likelihood of success" of the proposed experiments, among other considerations.

6.2 "Xenotransplantation of organ cultured foetal pig islets (pancreas) in cynomolgus monkeys"

In this study, ITN5, 37 cynomolgus monkeys received pancreatic islet cells from unborn piglets, either transgenic or of normal genetic status, between September 1995 and February 1996. Pancreatic islet cell implants have been touted as a possible treatment for patients with diabetes, the hope being that the porcine islet cells can stimulate the production of insulin, which is lacking in diabetics. However, this study was designed to examine solely the rejection of the islet cells and whether this could be overcome by the use of Imutran's hDAF pigs and immunosuppressive treatments. Imutran [REDACTED] remarked in a document produced in November 1994: "This is potentially an enormous market." He continued:

"Imutran has no expertise in the fields of Islet transplantation but has been approached by 3 different groups ([REDACTED]) offering to undertake primate studies (with Sandoz¹⁶⁰ funding)... In discussions with [REDACTED] it has been arranged for [REDACTED], of the [REDACTED] in Australia, to come to Cambridge on a sabbatical to study primate transplants for foetal transgenic pigs. The protocol for these experiments is attached."¹⁶¹

¹⁵⁸ "Xenogeneic transplantation", *British Medical Bulletin* 1997; 53 (No.4): 915.

¹⁵⁹ As above and "Current status of xenotransplantation", *International Journal of Cardiology* 62 Suppl. 1 (1997): S37-S38.

¹⁶⁰ Sandoz was the Swiss-based multi-national drug company that was funding Imutran's work and subsequently bought Imutran in 1996. The following year, Sandoz merged with Ciba to form Novartis.

¹⁶¹ See Files [REDACTED]

Presumably, ITN5 was the result of this collaboration. Having cut open the monkeys' abdomens, fragments of foetal pig pancreas supplied by Imutran were implanted beneath the membrane surrounding the kidneys. Following transplantation, some primates were given immunosuppressants while others were not, in order to study the differing patterns of rejection. Each group was sub-divided again between recipients of transgenic and non-transgenic foetal pig pancreatic islet cells.

The monkeys were sacrificed at different points following transplant: 7, 28, 41, 57, 65 and 90-odd days. The most common observations noted were "quiet" or "No abnormalities detected." However, the primates who were subjected to immunosuppression were often seen huddled or suffering from diarrhoea as the study progressed. Vomiting, another side-effect of immunosuppressive drugs, was also noted on occasions. Wound breakdown was another hazard, with blood seeping from the wound of W421m on day 1. Other clinical signs included unsteadiness, congested breathing, sneezing and nasal discharge, slow laboured movement, grating teeth, piloerection, swelling around the eyes, "swollen stomach wound seeping blood", "liquid faeces containing blood", blood around nostrils, "very quiet".

Although most animals appear to have been killed at a pre-set point, some seem to have been euthanased because of their suffering (W458f, W760f, W759m, X52f). W762f was found dead in her cage on day 19 having been quiet and huddled, and suffering diarrhoea and vomiting. The next transplanted animal, W774f was also killed by the drugs and found dead in her cage, this time on day 18. She had suffered from diarrhoea, sickness and had been unable to move freely.

This study, for similar reasons to ITN3, had also been deemed by Imutran to fail to comply with Good Laboratory Practice.

6.3 Bone and cartilage xenografting

Two studies transplanted pig bone (from transgenic and non-transgenic animals) into the tails of cynomolgus monkeys. In the first study, **ITN8**, which was performed between February and July 1996, 12 primates were transplanted and killed after 90 days for dissection. The second study, **ITN15**, consumed 18 monkeys between January and April 1997; these were put to death and autopsied after 60 days. Six of the 18 animals received bone grafts from cynomolgus monkeys so that a comparison could be made between the reactions to the three different classes of bone graft. Imutran claim that the research was conducted "with a view to assessing such bone as an alternative to human allograft." However, Imutran seem to have lost interest in this research after the two studies.

During ITN8, the monkeys were housed in cages either singly or paired up. ITN15 saw the monkeys confined alone for 60 days in squeeze-back cages measuring just 73cm wide, 82cm deep and 100cm high. During the study, blood samples were taken three times a week and the monkeys were sedated and anaesthetised at regular intervals in order that a biopsy sample could be taken from the tail for investigation.

The lack of immunosuppression, the peripheral function of the xenograft and the absence of major thoracic or abdominal surgery meant that the side-effects of the experiment were often not as marked as those suffered in organ xenotransplantation studies. However, for the first week or two after the procedures, diarrhoea was observed on several occasions and the monkeys were often seen quiet and huddled. The animals also regularly turned purple as a result of the dyes administered prior to biopsies of the tail.

During ITN8, W17m appeared to be in particular distress, and was observed “quiet and huddled” and “unsteady when moving”. He was also seen to be suffering “whole body tremors” and exhibiting “stereotypic activity”, where movement and activities are constantly repeated – a sign of mental disturbance.

Wound breakdown was another complication of surgery that lead to adverse effects for some of the primates. For the first few days after transplant, the wound on W16f’s tail was open and broken down. W22f experienced similar problems. W30f exhibited piloerection for several days during the post-transplant period, and blood spots were found on the bottom tray on day 24.

In ITN15, X401m’s tail wound was bleeding on day 15. Piloerection was also observed in some of the animals in this study.

Between May and July of 1996, 12 cynomolgus monkeys were transplanted with either transgenic or non-transgenic pig cartilage into their knees. This study, **ITN10**, was a one-off, although the study report claims that its purpose was to assess transgenic porcine cartilage as an alternative to human cartilage. The monkeys were kept alive for 30 or 60 days, at which point they were killed and their knee joints removed for examination.

The animals were housed in groups of three in steel and ‘printboard’ squeeze-back cages measuring 78 cm wide, 103 cm deep and 230 cm high. Blood samples were taken three times a week.

In the absence of immunosuppression, the most noticeable effect of the procedure on the animals was their impaired mobility, with the knee often swollen or sometimes bruised. Animals were occasionally observed to be quiet and huddled, or with loose faeces.

6.4 “Administration” and toxicity studies

Eight studies involving 59 primates sought to assess the effectiveness and toxicity of various immunosuppressant treatments for intended use in conjunction with xenotransplantation procedures.

The aim of the first of these studies, **ITN14**, which took place during September and October 1996, was to assess the [REDACTED] in depleting naturally-occurring antibodies in cynomolgus monkeys which would

normally contribute to an attack on transplanted pig cells (also referred to as ‘anti-pig antibodies’).

Two monkeys were used in the study, and each was housed singly in steel and printboard squeeze-back cages measuring 78cm wide, 103cm deep and 230cm high. Each of the monkeys was administered by intravenous injection a dose of [REDACTED] and then given a lethal injection 28 days later for post mortem studies.

[REDACTED] is not thought to be particularly toxic, and is described as an “immune response modulator” rather than an out-and-out immunosuppressant, thus no adverse effects were noted for the first animal. However, the second animal suffered an abscess of the eye, although this appears to have been treated successfully.

ITN22 was a similar study, but this time [REDACTED] was tested. [REDACTED] is a component of [REDACTED]. Some abnormalities were detected during study ITN14 through blood testing, so this experiment was performed to investigate which component of [REDACTED] was responsible. One of the two animals used was noted to be unsteady after dosing. Both were killed by lethal injection on day 28.

ITN20 used six monkeys to test the effects of an immunosuppressant, [REDACTED], on platelet function in the primates. Platelets are blood cells that help to form clots. This study was carried out because a previous porcine kidney transplant experiment (ITN12) had caused thrombocytopenia (depletion of platelets) and subsequent haemorrhage. Imutran wondered whether this effect was due to the immunosuppressive regime alone, and [REDACTED] in particular. The six monkeys were dosed with [REDACTED], [REDACTED] and [REDACTED] (mimicking the treatment received in the context of xenotransplantation experiments) over ten days during November and December 1996, before being killed and autopsied.

This is the summary of clinical signs found in the final draft study report:

“Group 1

There was a gradual increase in the incidence of quietness and subdued behaviour as the study progressed. For the male, this began around Day 7, while for the females, quietness was first observed at Day 3. For the male, piloerection was seen from Day 8 and the animal was huddled with body tremors on Day 9. Salivation at dosing was seen on Day 10 only. Body tremors were also seen for female 343 on Days 9 and 10.

Group 2

Animal 344 male - The animal was quiet from Day 2, becoming subdued and huddled from Day 3. The animal vomited at around 1 hour after dosing on Day 4, and 6 minutes after dosing on Day 5. Salivation associated with dosing was seen on Days 5 and 6. From Day 6, the animal was paired with animal 345 female due to its condition and low body temperature (see below). The animal continued to be quiet, huddled and/or subdued until the end of the

study. The animal passed liquid faeces from Day 8; piloerection was seen from Day 8.

Animal 345 female - The animal was quiet from Day 2, becoming subdued, with piloerection from Day 3. On Day 6, the animal was examined by a Veterinary Officer because it had become dehydrated and because of prolonged menstruation. 10 ml Haemocel and 30 ml Hartmanns fluid were administered intravenously; extra food supplements (including blackcurrant drink) were offered and the animal was paired with 344 male (as noted above). The animal continued to be quiet and huddled with occasional piloerection; on Day 10, liquid faeces were seen and the animal was subdued.

Animal 346 female - Piloerection, quietness and/or subdued behaviour were seen daily from Day 2. Huddled posture was noted on occasions from Day 7. From Day 6, the animal was offered extra blackcurrant drink because of slight dehydration and low temperature, and from Day 7, the animal was grouped together with animals 344 and 345. Liquid faeces were seen on Day 9, and the animal vomited at dosing on Day 10.”

ITN23 and **ITN24** both consisted of the administration of a substance called [REDACTED] which was similar to the [REDACTED] administered in study ITN14.

In ITN23, six monkeys were injected with the [REDACTED] and thereafter blood samples were taken to track the levels of [REDACTED] and anti-pig antibodies. Two animals received the [REDACTED] with the addition of a radiolabelling substance. When these two were killed 12 hours after administration, the radioactivity in their organs was measured to discover the distribution of the [REDACTED] throughout the body. The remaining four were killed on day 2. No adverse effects were reported.

ITN24 saw the administration of a variety of [REDACTED] over a 69 day period between August and October 1997 to five monkeys to see if they effectively depleted anti-pig antibodies. Once again, no adverse effects were reported, although all the monkeys were killed and dissected at the end of the experiment.

In the same vein, study **IAN006** entailed the administration of similar compounds, called [REDACTED], to 16 monkeys over a 28 day period during November and December 1997. This was an unusual study insofar as the monkeys did not appear to be substantially physically affected by the test substances and they were not slaughtered at the end of the study.

IAN014 similarly dosed 16 monkeys with [REDACTED], but this time over a 69 day period from March to May 1998. Four of the animals were killed at the end of the administration period for “terminal investigations” – dissection and examination of tissues and organs.

The final study in this group, **IAN021**, killed six monkeys at the beginning of February 1999 having dosed them with a [REDACTED] for six days to try to

determine what volumes of the substance were required to reduce substantially the levels of anti-pig antibodies in the primates' blood.

6.5 Heterotopic kidney (renal) xenotransplantation

The largest category of study commissioned by Imutran to be conducted at HLS involved the transplantation of porcine kidneys into the abdomens of cynomolgus monkeys. The study reports reveal that 211 monkeys died in such experiments from July 1995 through to June 1999, and probably beyond this date. In addition to the 19 reported studies, at least four more took place for which final draft reports have not become available. The evidence points to such studies continuing up to – and possibly beyond – February 2000.¹⁶²

The notes of a meeting held at HLS on 28th April 1995, three months before the first kidney study began, explain how the programme of renal xenotransplantation research came about.¹⁶³ At the time, the drug company Sandoz were supporting Imutran's research with both finance and advice: Sandoz subsequently bought Imutran in April 1996. Up until the time of the April 25th meeting, none of the primate vivisection procedures had been life-supporting, but it was to this more significant stage that Imutran wished to move their research. However, because the "Home Office regard[ed] heart transplants in primates as severe procedures," it appears that "Sandoz... suggested kidney transplants" and "the Home Office will attempt to get these classified as moderate procedures."

The following examination of the effects of these procedures on animals will demonstrate that a 'moderate' categorisation for their severity would be hard to credit. Furthermore, it would be particularly disturbing if it was to be proved in a subsequent enquiry that the Home Office's role in attempting to classify these procedures as 'moderate' facilitated the licensing of a set of experiments that may not have been permitted if a more reasonable assessment of their severity had been made.

The first renal transplantation study, **ITN4**, took place from July 1995 through to May 1996, during which time 22 cynomolgus monkeys were transplanted and subsequently died. All but one of the animals were captive-bred in Mauritius and imported through the now-defunct primate supply company [REDACTED]. The other animal came from [REDACTED] in the Philippines.

In the surgical procedure, the left piglet kidney was implanted into the monkey's abdomen, followed by the removal of both native kidneys. This left the porcine kidney playing a life-supporting role though still heterotopically (i.e. abnormally) positioned. The implantation process was a difficult operation requiring extensive microsurgery and close attention to the position of the kidney, as slight differences in placement could avoid or promote thrombosis (clots) in the blood vessels leading to the organ. The right kidney from the transgenic piglet was kept in a cool solution in readiness for transplant in case of problems with the left kidney. Immunosuppression

¹⁶² See Files [REDACTED]

¹⁶³ See File CY14.1.

readiness for transplant in case of problems with the left kidney. Immunosuppression in this study comprised of the familiar combination of [REDACTED]

A document relating to a meeting held on 19th December 1995 to review pig to monkey kidney transplantation¹⁶⁴ admits “this animal model has not been without its difficulties”: appendix 1 of the study report suggests that this was an understatement.¹⁶⁵ Once again, the study generated a high technical failure rate. Seven of the primates failed to survive longer than a day – and were classified as technical failures. A further three animals died after one day, with the same number succumbing after two days. Four more did not achieve double-digit survival periods, leaving only five out of the 22 living longer than ten days. The maximum survival time was 35 days. The sponsors of the study, Imutran, determined that the study was not performed in compliance with Good Laboratory Practice, thus potentially both undermining the integrity of the data produced as well as rendering the suffering and sacrifice of these higher primates even more futile.(see section 7.3)

The clinical signs at appendix 11 reveal a familiar tale. The first three primates all died after one day. **W435m** was noted to be “distressed” before he was “sacrificed.” **W437m** was unsteady, quiet and huddled on his last morning.

W399m was one of the few longer survivors, living for 28 days before finally succumbing to anaemia, according to a published paper.¹⁶⁶ In fact, fatal anaemia was a constant problem, and appeared to be caused by the inability of the porcine kidney to produce the correct form of the hormone [REDACTED], which is necessary to stimulate the production of red blood cells in primate bone marrow.¹⁶⁷ Following post-mortem, W399m was also found to have suffered a thrombosis in the renal vein,¹⁶⁸ and a “grossly enlarged kidney”¹⁶⁹ that had swollen massively from 29g to 168g.¹⁷⁰ He had also endured three episodes of oliguria (abnormally low urine output), two of which lasted three days. This type of event is a sign of renal failure, and also leads to a build-up of immunosuppressive drug residues which have the potential to cause further complications associated with drug toxicity, including bone marrow suppression.¹⁷¹ Renal failure itself results in an accumulation of waste products such as urea in the blood.¹⁷² This in turn leads to “nausea, vomiting, lethargy, drowsiness, and eventually death.” Renal failure was a recurring conclusion to the lives of the primates used in all of these studies.

¹⁶⁴ See Files in [REDACTED]

¹⁶⁵ See File [REDACTED]

¹⁶⁶ See File CY16.1. Anaemia is a deficiency in the quantity of oxygen-carrying haemoglobin in the blood.

¹⁶⁷ “Life-supporting pig-to-primate renal xenotransplantation using genetically modified donors.” *Transplantation*, Vol. 65, No. 12, 1998: 1588-9.

¹⁶⁸ “Life-supporting pig-to-primate renal xenotransplantation using genetically modified donors.” *Transplantation*, Vol. 65, No. 12, 1998: 1586.

¹⁶⁹ See File CY16.1.

¹⁷⁰ See File [REDACTED]

¹⁷¹ See File [REDACTED]

¹⁷² Urea is a waste product of protein metabolism, and is formed in the liver from ammonia and carbon dioxide. Blood urea levels were measured and recorded for each animal, and the data is found in Appendix 8 - “Biochemistry”. The higher the levels of urea, the more pronounced the kidney failure. The data clearly demonstrates episodes of swift accumulation of urea for the monkeys.

W399m appears to have been quiet throughout his last 28 days of life. On day 8, his eyes and muzzle were noted to be swollen, and “white frothy vomit” was found in his tray. His urea levels were tremendously high from day 20 until his death, ranging between 260 and 365mg/dl (compared to a normal reading of 35-55).

W556f lasted 16 days after the xenotransplantation operation. She was also destroyed because of anaemia, and suffered oliguria. The post-mortem revealed acute vascular rejection (AVR) and microabscesses on the kidney. Once again, the kidney had ballooned, weighing in at 115g at necropsy having initially weighed only 23.5g. From day two to five she veered from unsteadiness to agitation and vocalisation. On day 8 her urine was noted to be very dark, and from that point onwards she was quiet. Eventually, she was very quiet and huddled with swelling under the eyelids when she was put down on the sixteenth afternoon.

W562f was killed after 13 days, also due to anaemia. For the last four days she was quiet and blood clots were observed passing through her vagina. The post mortem found large blood clots¹⁷³.

Two days after transplant, **W560f** was killed. She had been lying on the cage floor and the grafted kidney had failed to produce urine after the operation had finished. **W548f** survived six days. For part of this time she had been reluctant to use her swollen legs, and had produced green vomit on day two. The morning of her sacrifice due to renal failure and a ureteric obstruction (blockage of the ureter, which carries urine from the kidney to the bladder), she was found “lying on the cage floor” and subsequently “very weak and unsteady when moving.”

On **V337m**’s seventh and final day, he was observed:

7 am	Very quiet and subdued. Occasional trembling. Appears unsteady.
pm	Huddled. Unwilling to move. Collapsed state. Sacrificed.

His kidney had suffered AVR and failed.

T381m also suffered AVR and renal failure before being killed on day 8. He was quiet and huddled for most of his post-transplant period. Shaking was observed throughout day six. On the day of his sacrifice his notes state: “Little or no movement when stimulated.”

The longest survivor, at 35 days, was **T397m**. But his ‘borrowed time’ came at a heavy price. For the last 16 days of his life, he appears to have been very poorly indeed:

18 am	Quiet but alert. Occasionally huddled.
pm	Quiet, huddled. Loose/normal faeces.
19 am	Alert but reluctant to move. Loose faeces. Some vomit in tray.
pm	Alert but reluctant to move. Loose faeces. Some vomit in tray.
20 am	Quiet, huddled, reluctant to move. Vomit and liquid faeces in cage.
pm	Inactive, huddled on cage floor/sitting posture.
21 am	Quiet, huddled on perch, reluctant to move. No reaction to external

¹⁷³ See File CY16.2.

		stimuli, vacant appearance. Clear nasal discharge. Liquid faeces in cage.
	pm	Quiet, huddled on perch, reluctant to move. No reaction to external stimuli, vacant appearance. Clear nasal discharge. Liquid faeces in cage. Collapsed following administration of parenteral dosing. Some recovery, very quiet, sitting holding perch. Little interest in surroundings.
	22 am	Quiet and huddled. Reluctant to move. Constant grinding of teeth. Liquid faeces.
	pm	Quiet, huddled but alert. Liquid faeces.
	23 am	Quiet but alert. Liquid faeces.
	pm	Quiet, huddled but alert. Liquid faeces. Limited movement. Swelling in legs at dosing sites
	24 am	Quiet, huddled but alert. Liquid faeces. Clear nasal discharge.
	pm	Quiet, huddled, reluctant to move. No reaction to external stimuli. Loose/liquid faeces.
	25 am	Quiet, huddled but alert. Liquid faeces.
	pm	Quiet but alert. Liquid faeces.
	26 am	Quiet but alert. Liquid faeces.
	pm	Quiet but alert. Liquid faeces.
	27 am	Quiet and huddled on cage floor. Clear nasal discharge.
	pm	Quiet and huddled on cage floor. Clear nasal discharge.
	28 am	Quiet, huddled but alert. Liquid faeces.
	pm	Quiet, huddled but alert. Liquid faeces.
	29 am	Quiet, huddled but alert. Liquid faeces.
	pm	Quiet, huddled but alert.
	30 am	Quiet but alert. Loose faeces. Vomit in cage.
	pm	Quiet but alert. Loose faeces. Vomit in cage.
	31 am	Quiet, huddled but alert. Liquid faeces.
	pm	Quiet but alert. Sitting on cage floor.
	32 am	Quiet, huddled but alert. Sitting on perch. Loose faeces.
	pm	Lying on cage floor.
	33 am	Lying down following blood sampling. Liquid faeces.
	pm	Quiet but alert, huddled. No faeces.
	34 am	Very quiet, huddled but alert. Swelling under both eyes. Loose faeces.
	pm	Very quiet, huddled but alert. Swelling under both eyes. Loose faeces.
	35 am	Quiet, huddled, alert at times. Appears weak. Seen to collapse. Sacrificed.

The protracted and tortuous ordeal of these primates as they died of renal failure or anaemia raises fundamental moral questions about the justifiability of this research. However, it also reignites concern about the adherence to regulations of these experiments. In particular, the experiences of W399m and T397m are reminiscent of the fate of baboon W205m, whose clinical signs revealed severe suffering for ten days before euthanasia. The question is, did this signify a breach of the severity limit supposedly imposed upon the experiment? If not, then the severity limits must have been set so high that they offered virtually no protection to these animals. Either way, both incidents provoke grave concerns not only for the sake of the animals victimised, but also for the effectiveness of the regulatory system which, rather implausibly, speaks of “protected animals.”¹⁷⁴

¹⁷⁴ Animals (Scientific Procedures) Act 1986, Section 1.

W151m's survived just two days post-transplant. He seems to have hardly moved in his two days of life post-transplant, and his 'unusual posture' was repeatedly noted.

The clinical record of the 21 post-transplant days of **V7m**'s life raises the same concerns as the cases of **W399m** and **T397m**. Producing bloody urine, he appeared "uncomfortable" and was observed grinding his teeth. On day ten he was seen crouched in the corner of his cage, salivating and retching. Eventually he was killed on day 21.

The last animal to be vivisected in this study, **T407m**, lived for six days. On his last day it was noted: "Appears cold. Extremely pale and very weak. Sacrificed."

This study was partially written up and published as a paper: [REDACTED] "Life-supporting pig-to-primate renal xenotransplantation using genetically modified donors", *Transplantation*, Vol. 65, No. 12, 1998: 1584-90. Only seven of these animals appear in the published paper – selected from the eight longest survivors. Thus Imutran can claim in the paper a median survival time of 13 days, but for the study as a whole the median survival was two days and the mean survival 6.7 days. The same selectivity with regard to the primate recipients appears in one of the authors of the study, [REDACTED], in his proposed MD Dissertation submitted to the [REDACTED]¹⁷⁵

The main aspiration of subsequent studies was to develop an immunosuppressive regime that was simultaneously more effective and less toxic. In particular, Imutran were looking to [REDACTED] or through performance of a splenectomy (removal of the spleen) on the recipient.¹⁷⁶

The next study, **ITN12**, took place during July and August 1996, and involved the addition of [REDACTED] to the immunosuppressive regimen. None of the six monkeys used in this study survived longer than eight days. The clinical signs record the harrowing ordeal of the primate recipients. For example, **W39m** was predominantly quiet throughout his last eight days, and suffered piloerection, vomiting and diarrhoea. On day 7 he was noted to be "Quiet, huddled with head between legs, loose faeces, semi-digested vomit, very subdued, diarrhoeic." **V510f**, **W43m** and **V484f** all collapsed prior to being killed. Blood-stained urine and vomit was also noted during this study. Imutran suspected that the [REDACTED] had caused internal haemorrhaging in the recipients and subsequently organised another experiment (**ITN20**) on six monkeys to try to test this theory.

From August to November of 1996, study **ITN13** killed eight monkeys to investigate the effectiveness of the additional immunosuppressant [REDACTED] instead of [REDACTED]. All the animals were dead within eight days. Among the worst episodes, **W14f** was found dead in her cage on the eighth morning. On day four, **X523m** was observed: "Quiet but alert, loose faeces, vomit in tray, listless, lying in cage and possibly exhibiting abdominal discomfort, frank haemorrhage from penis." **X527m**

¹⁷⁵ See File CY17.2.

¹⁷⁶ See File CY17.3, and "Life-supporting pig-to-primate renal xenotransplantation using genetically modified donors." *Transplantation*, Vol. 65, No. 12, 1998: 1589.

was in a similar state on day four, though without the haemorrhage. **X529m** was literally laid out by the procedure before being killed on day two.

And so the research continued relentlessly. **ITN16** tested [REDACTED] on seven monkeys in Winter 96/97. In **ITN18**, a control study which used non-transgenic pig kidneys, Imutran were surprised that two of the six primates survived a month post-transplant. Imutran persisted with [REDACTED] in Study **ITN21** in early 1997, but none of the twelve monkeys lived longer than twelve days. On her last day, **X538f** was seen lying down or sitting hunched with her head down, haemorrhages all over her body. Many of the other animals were also noted to be suffering from these haemorrhages. **X535f** was found dead on her cage floor on day six. **X666f's** nightmare was evidenced by the observation of “nystagmus” - rapid involuntary movement of her eyes.

The next study, **ITN26**, included an innovation: splenectomy. This was performed on 17 monkeys from March to July of 1997. The removal of the animals' spleens appears to have helped achieve longer survival times, with five of the animals living between 39 and 78 days post-transplant. However, apart from these and another animal who survived 18 days, none of the others saw their tenth day. The overall mean survival of the group was just under 20 days. **Y215m** seems to have been ill during his entire 39 day survival period. The longest survivor **X530f**, was noted to be suffering from an “extremely distended” abdomen on day 65. This sign was repeatedly noted throughout her last 13 days before she was killed. She turned out to be the longest surviving primate with a life-supporting xenograft for whom study reports have been acquired.

A letter sent by Imutran's [REDACTED] to the local Home Office Inspector, [REDACTED], refers to the fate of seven of the ten animals transplanted in study **IAN009** in January 1998.¹⁷⁷ The animals had been splenectomised, and were to be administered additional immunosuppressants in the form of [REDACTED] and a substance called [REDACTED] (known as [REDACTED] or [REDACTED]). [REDACTED] informs [REDACTED]: “You will note that we have experienced an unusually high level of technical failures...” The letter reveals that technical failures are not limited to deaths within 24 hours of transplant. Rather, a number of complications arising from the surgical procedure can cause death several days later. Bearing this in mind, the true technical failure rate may be higher than apparent from the study reports.

[REDACTED] discloses that two of the animals, **Y256m** and **Y148f** died as a result of errors in the anaesthesia procedure:

“...[T]wo animals that survived surgery well Y256 and Y148 were prescribed [REDACTED] at very high doses which resulted in the animals being over sedated which ultimately lead to a failure to recover from anaesthesia and their ultimate euthanasia due to the relatively long half life of [REDACTED]”

The clinical signs reveal that **Y148f** was found unresponsive and lying on the cage floor on the morning following transplant – she was then destroyed. Blood was noted around **Y256m's** penis and scrotum on his first day post-transplant. For the next three days he must have made a pitiful spectacle: slumped against the front of the cage,

¹⁷⁷ See Files in CY18.

drifting in and out of consciousness, his turmoil punctuated by bouts of vomiting and salivation. He was finally killed on the afternoon of day 4.

■■■■■ letter continues to explain the reasons behind other failures in this study:

“The second arm of the problem relates to recent changes in our surgical team [these are not specified] and the lull in surgery from 2 December 1997 to 13 January 1998, as you know in the past we have experienced increases in technical failures when the surgical team are made to perform stop-start surgery, and this has certainly contributed to this unacceptable situation.”

Each of these excuses – the anaesthetic errors, the personnel changes and timing of surgery – are ultimately the responsibility of Imutran. The company should have ensured that the optimum conditions for the conduct of these studies were in place; in fact, the adherence to such conditions is required under the terms of the Home Office licence. Once again, deep concern must be expressed about the effectiveness of the Home Office’s response to ■■■■■ correspondence.

In his letter, ■■■■■ goes on to describe the outcome of the surgical failures:

“Animal Y225, whilst it survived 8 days was euthanased due to pancreatitis which is a known complication of splenectomy. Animal Y254 was euthanased before recovery from surgery due to renal vein thrombosis.”

Ultimately, it is the animals that pay the price for these difficulties: **Y225f** appears to have been ill throughout her eight days. Finally:

8	am	Appears subdued and huddled on ladder, fairly alert when stimulated, reluctant to move, dark faeces. Later; very subdued and unsteady, vacant expression and disinterested in surroundings, abdomen distended.
	pm	Sedated; struggling to breathe whilst sedated, yellow fluid draining from nostrils. Sacrificed for humane reasons

Another animal, **Y245m** was killed on the table because neither of the transgenic pig kidneys would perfuse with blood during the surgical procedure. Imutran responded to this problem by pledging to provide a reserve piglet on surgery days whenever possible. However, if the second piglet was not used, s/he would simply be killed because his/her microbiological ‘cleanliness’ would have been compromised by transport to HLS. Hence the intrinsic difficulties of these procedures result in the exacerbation of the costs endured by the animals involved.

A summary of the results of this study attached to another letter to the Home Office reveals two more deaths due to “technical complications”. **Y251m** and **Y249m** were both killed after seven days having suffered ureteric obstructions.¹⁷⁸

¹⁷⁸ See File CY19.3.

Because of the few “informative cases” gained during IAN009, Imutran wished to be permitted to try this combination of immunosuppressants on more monkeys.¹⁷⁹ Analysis of the study reports suggests that this request was turned down by the Home Office.

The danger to the cynomolgus monkeys did not only stem from the experiments. The minutes of a Progress Review Meeting held on 29th January 1999 state: “... cynos that are deemed terminally unsuitable [for surgery] will be culled.”¹⁸⁰ However, approximately two months later, an Imutran draft document “Responses to Comments Raised by the Primate Sub-Committee” (para 4c)ii) states: “However should animals prove unsuitable for surgery for any reason they will be given to HLS for use in other projects.”¹⁸¹

Study IAN020

A batch of informative documents discusses the fate of monkeys used in study **IAN020**, which took place from November 1998 through to January 1999.¹⁸² Taken with the final draft study report, the picture we have of IAN020 is the most complete of any of the cynomolgus monkey studies. It was during the conduct of IAN020 that Imutran’s ██████ wrote to HLS to complain vociferously about a quadruple drug overdose incident and the failure to take a blood sample at the correct time (see section 7.8 for full analysis of these incidents, including the clinical signs). One primate, **A178f**, “was exposed to a dose of ██████ which was four fold higher than recommended,” and died the next day.¹⁸³ The animals whose blood sample was taken at the wrong time, **A464m**, had to be destroyed after four days in any case: the surgical team had left a swab inside him, which caused his spleen to go septic.¹⁸⁴

The first transplanted primate, **A170f**, survived the longest of the twenty monkeys used in the study – 60 days. She endured the conditions frequently associated with these experiments: body tremors, piloerection, diarrhoea. She was, understandably, also noted to be threatening and aggressive on occasions. Puffiness and swelling around her eyes was observed throughout her last twenty days. During her last few days she was huddled and apparently reluctant to move. Before she was killed, she was found lying on the floor of her cage, unable or unwilling to move, and excreting liquid faeces. The pathology reports reveal that her kidney had undergone “massive AVR [acute vascular] rejection” as well as Grade 3 (the most severe) cellular rejection (CXR).¹⁸⁵

¹⁷⁹ See Files CY18.2 & CY19.1.

¹⁸⁰ See File CY20.1.

¹⁸¹ See File CY21.3.

¹⁸² See Files in HLSAPP7A, HLSAPP7B and CY22.

¹⁸³ See file HLSAPP7C.1.

¹⁸⁴ See files CY22.2, HLSAPP7A.3 & HLSAPP7B.2.

¹⁸⁵ See files CY22.2 and HLSAPP7B.2.

Next on the table was **A166m**. He was relatively lucky because he was not transplanted because of a new form of technical failure: the piglet kidney was frozen during storage.¹⁸⁶ The clinical signs say he died in surgery.

A176f remained alive for 33 days after transplant. This was the diary entry for her last day:

am	Alert but quiet, huddled on ladder, puffy face especially around eyes, loose faeces.
pm	Noted prior to sedation: prolonged periods of huddled, unsteadiness and reluctance to move. Sedated and euthanased.

The pathology reports note that her grafted pig kidney had also undergone AVR and another form of rejection called cellular xenograft rejection (CXR), though this time to Grade 2 rather than 3. However, she also had a small haemorrhage in her lungs and an infected spleen.

A week after surgery, Imutran attempted to pair transplanted animals with non-transplanted monkeys during the daytime to try to achieve longer survival times. In her last few days, **A167f** huddled her partner on several occasions as her condition deteriorated. She was so sick that she was reluctant to move and suffering from diarrhoea, limb tremors and swelling around her eyes and abdomen. Eventually, on the afternoon of day 31, she was euthanased. She was: “Very quiet, huddled oedematous [fluid-filled] swelling around eyes, reluctant to move, unsteady.” The pathology findings reveal that her xenotransplanted kidney had undergone Grade 3 AVR and CXR. The attack on her kidneys had been compounded by a severe infection of Cytomegamavirus (CMV), a member of the herpes family of viruses. The virus had also caused pneumonitis – inflammation of the lungs – and had also infected her gut.

CMV infection was, in fact, a significant feature of this study. An Imutran meeting on 22nd January discussed the case of **A457m**, who had died in a terrible state after 29 days:

am	Alert, eyelids partially closed, swollen abdomen, loose faeces, reluctant to move even when stimulated.
pm	Noted prior to sedation: very distressed and having difficulty breathing, mucous membranes blue/grey in colour, animal collapsed. Sedated and euthanased.

The meeting noted that he had been infected with CMV which had caused pneumonitis and was thought to have attacked the lining of his stomach. There was haemorrhaging and congestion of his kidney, and the blood vessels and filtering tubes of the organ were also inflamed.¹⁸⁷

¹⁸⁶ See files HLSAPP7B.2 and clinical signs for IAN020 (p.136).

¹⁸⁷ See File HLSAPP7A.3.

A452m was killed after 16 days. His post-mortem revealed that he was also extensively infected with CMV. One scientist at the meeting suggested that it was this virus which had caused a severe and fatal inflammation in the kidney. The organ had also undergone CXR.

Four other recipients with evidence of CMV infection were **A461m**, **A459m**, **A463m** and **A462f**.

A461m lived 29 days. His kidney was diagnosed as having been rejected and he also suffered pneumonitis. Yet again, his last few days appear to have been dreadful:

28	am pm	Eyelids partially closed, huddled on ladder, licking sore on tail. Alert, occasional gentle activity, huddled, slow movements, no faeces.
29	am pm	Huddled on perch, raises head only when stimulated, very unsteady when stimulated to move, bruising on both forearms, thighs and scrotum appear swollen, dry scab-sore on tail. Noted prior to sedation: below normal body temperature, collapsed posture. Sedated and euthanased.

After he had survived 43 days, A459m was “euthanased due to worsening condition with bilateral effusion and respiratory failure”:

43	pm am pm	Quiet and huddled on perch, loose faeces, breathing appears fast and shallow, reluctant to move even when stimulated, appears drowsy, face and area around wound swollen. Quiet but alert, loose faeces. Noted prior to sedation: (observed following an episode of collapse) rapid breathing, very quiet and having difficulty balancing, not responding to stimuli. Sedated and euthanased.
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‘Bilateral effusion’ signifies the filling up of the lungs with fluids, possibly as a result of the monkey’s pneumonitis brought on by CMV infection. In addition, he had suffered a “high incidence of diarrhoea” and rejection of the kidney.

The CMV infection was thought to have caused pneumonia in A463m, who died after 35 days. The kidney was inflamed, possibly due, once again, to the CMV, and had undergone rejection. The renal vein was clotted and he had become dehydrated due to “gastrointestinal loss”, i.e. diarrhoea.

A462f was the last animal transplanted in this study. She died three days later due to a “technical failure” rather than the effects of CMV infection. The clinical signs record her awful condition:

1	am	Alert, sitting up but minimal activity, lethargic, liquid bile like vomit.
	pm	Laying on stomach, scratching abdominal area.
2	am	Lying down, reluctant to move, alert when stimulated, no faeces.
	pm	Sitting upright at front of cage on floor, alert but reluctant to move, no faeces.

3	am	Noted prior to sedation: alert but subdued, vomited, very liquid faeces, very reluctant to move even when stimulated. Sedated and euthanased.
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Imutran believed that the CMV infections found in this study did not originate from the pigs and could not have been transmitted by handlers as it is a blood-borne organism. CMV infection is a complication in conventional transplantation, as it appears to become virulent as a result of immunosuppression. The devastating effects of “the higher than usual incidence of infection” in this study prompted Imutran to consider preventative treatment in the form of anti-viral drugs. However, one of the potential side-effects of such therapies is gastro-intestinal toxicity, a situation Imutran had already encountered with the administration of the drug [REDACTED]. Despite this, “it was suggested that it probably would not add significantly to **the already prominent levels of diarrhoea seen in these recipients**,” and one of Imutran’s researchers was delegated to obtain a paediatric formulation of the drug [REDACTED].¹⁸⁸ (emphasis added)

One set of meeting minutes describe the condition of A469m on day 14:

“Currently being treated for a rejection episode. Has had one week of diarrhoea with no positive culture results and has been unresponsive to treatment.”¹⁸⁹

Three days later he was dead.

CMV was not the only source of infection of the primates in this study. **A451m**, who lived for 29 days, was found to be infected with *Balantidium*, a parasitic protozoa, which caused an inflammation of the colon. His pancreas was also inflamed, as was his kidney:

28	am	Quiet but alert, active when stimulated, dark loose/soft faeces.
	pm	Quiet but alert, grooming whilst in hammock, black liquid faeces.
29	am	Noted prior to sedation: alert but quiet in hammock, slightly puffy around eyes, reluctant to move when stimulated, liquid faeces. Passing urine very heavily contaminated with blood, hard swelling left side of suture line, very quiet, pained facial expression. Sedated and euthanased.

The incidences of infection to have emerged during these transplant procedures also rouse concern about adherence to Good Laboratory Practice (GLP). For one of the GLP principles states:

“At the experimental starting date of a regulatory study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study.”¹⁹⁰

¹⁸⁸ See File CY22.3.

¹⁸⁹ See File HLSAPP7A.1.

Yet another disorder also materialised in this study. The abbreviation PTLPD appears in the pathology findings for three of the animals. We deduce that PTLPD stands for *post-transplant lymphoproliferative disorders*, i.e. early lymph cancer. The issue of PTLPD was subsequently raised at a meeting held by the United States' FDA in June 1999 which focussed on the status of xenotransplantation research. At the meeting, Imutran reported that some of the monkeys they had experimented upon had been found at autopsy to have PTLPD. The cause of this nascent cancer had not been established, though two possibilities were mooted:

1. PTLPD could be caused by the immunosuppressant drug [REDACTED]. One theory suggests that cynomolgus monkeys are especially sensitive to this drug in this respect.
2. PTLPD could be due to a persistent cancer-causing virus in the source pig which has become active in the primate recipient.

In addition to technical failure, viral and protozoal infections, lymph cancer, kidney failure due to rejection, and severe diarrhoea, other complications arising from the surgical procedure accounted for some of the animals. There was, for instance, the aforementioned A464m, whose blood was sampled at the wrong time thereby hindering attempts to calculate a tolerable yet effective dose of immunosuppression. He died because of a foreign body that was left inside him at surgery – a swab. It caused his spleen to go septic, and in his last 24 hours, he was:

pm	Quiet and inactive resting on ladder reluctant to move, black loose faeces.
am	Alert but eyelids partially closed, huddled on cage floor, reluctant to move even when stimulated then moves very slow and unsteady, dark green liquid faeces. Sedated and euthanased.

A465m had to be euthanased primarily due to “problems with the wound site”¹⁹¹:

20	pm	Wound opening and seeping, bandaged, active and alert, no faeces.
	am	Quiet and huddled on top of ladder, becomes active when stimulated, liquid faeces. Noted prior to sedation: subdued and huddled, body tremors, eyelids appear closed, no movement even when stimulated, no faeces. Sedated and euthanased.

The list of hazards did not stop there. At the pathology meeting of 26th March, one of Imutran's surgeons, [REDACTED], “raised the point that out of 5 biopsies taken at surgery, there had been two cases of ureteric clot retention, which lead to renal failure and subsequent euthanasia of the recipients. [He] asked whether these risks outweighed the benefits of the data obtained from the biopsies.” However, Imutran management's

¹⁹⁰ Good Laboratory Practice Regulations 1999, Schedule 1, Part V, Section 2(2).

¹⁹¹ See File CY22.2.

desire to learn more about the rejection process through the performance of biopsies seems to have prevailed over this concern for the fate of the animals.

The impact of biopsies on the welfare of the animals was such a serious concern that, according to the minutes of the APC's October 1999 meeting (para. 7.4), Imutran were actually refused authority to conduct the biopsies. The minutes do not state the reason for this refusal, nor whether the ban on biopsies was a long-standing policy (which would obviously raise concerns about the legitimacy of conducting biopsies in study IAN020), or whether this refusal came after the IAN020 biopsies, perhaps in response to their lethal consequences. Unfortunately, Dr Maggy Jennings, a member of both the APC and the UKXIRA, reported that Imutran responded by taking their primate vivisection from the UK to Canada rather than accept this constraint on their manipulation of primates in the course of their experiments – a course of action that Jennings states was communicated to the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). The UKXIRA's reaction to such news would be interesting to discover.

There is an ironic aspect of Imutran's export of primate vivisection from the UK because of regulations in this country: their translocation was made possible only because the Home Office and MAFF have previously granted permission to export transgenic pigs from the UK in order that breeding colonies could be established overseas. It was these colonies that provided the raw 'material' for the relocated research programme and for possible human clinical use in the future.¹⁹²

The final significant matter to come to light in connection with study IAN020 concerns inconsistencies in the pathology findings for the animals. A letter from [REDACTED] to Imutran's pathologist based at [REDACTED], [REDACTED],¹⁹³ reveals that two separate meetings held to discuss the pathology of the primates generated conflicting diagnoses for nine of the twenty animals, leaving Imutran with the problem of deciding which diagnosis was correct and should be entered into the records. [REDACTED] complains: "Clearly this process is not satisfactory and I suspect jeopardises our ISO 9000 status."

Further Failures and "The Full Monty"

The two most recent renal transplantation studies referred to in the acquired internal documents are IAN012 and IAN022. No study report has been obtained for IAN012, but the minutes for a meeting held on 23rd April 1999 to review the study have emerged.¹⁹⁴ **Ten** animals are mentioned in the minutes, with **five** of them dying as a result of technical failures. Another primate "received a graft biopsy at day x, which then resulted in a clot in the ureter, which resulted in the animal being euthanased for renal failure." The informational benefits of biopsies appear to be undermined by the observation of the pathologist at the meeting, [REDACTED], who "stated that the biopsy appeared normal, where the graft in contrast was seen to have some AVR present with a cellular component." This seems to have provoked further doubts about

¹⁹² M. Woolf, "Transgenic pigs sent abroad for experiments," *The Observer*, 10 May 1998, p.7. "Ed Hall Investigates," broadcast on BBC5Live, Sunday 14th February 1999.

¹⁹³ See Files in HLSAPP7B.

¹⁹⁴ See Files CY23.1→CY23.3.

the justifiability of the biopsies: “██████████ questioned the value of the biopsy if an animal has to be euthanased due to a clot/bleeding from the biopsy site.” However, Imutran wanted to press ahead with biopsies: “It was the general consensus that the biopsies must be taken in order to learn more about the rejection process at various time points.” Another document recording the minutes of a “Progress Review Meeting” sheds more light on the motivation for the persistence with biopsies.¹⁹⁵ The meeting, held on 30th March 1999, discussed “goals” set for Imutran by their parent company Novartis. Presumably, these “goals” referred to progress in terms on improved graft survival periods. In order to achieve this, “overcoming AVR is now of primary importance”, which is where the role of the biopsies was thought to be vital: “the timely collection of graft biopsies is imperative to achieving this goal.”

The kidney grafts in the remaining four monkeys were all severely rejected. Yet another additional complication arose in this study: one of the rejection processes, cellular rejection (CXR) appeared surprisingly early in this study.

The final renal xenotransplantation study for which a study report has appeared was IAN022. This study was tastefully nicknamed the “Full Monty”, presumably in reference to the extensive range of immunosuppressive techniques employed, including splenectomy and various drugs. Despite this, the longest survival period was just 36 days. Apart from the suffering of the transplanted monkeys, the most disturbing aspect of this study is the high incidence of technical failures that occurred. An email from ██████████ Imutran’s ██████████ to ██████████, states: “We have performed 20 Full Monty’s, with over 50% TF’s.” ██████████ responds later that day, 13th May 1999, by circulating an email to Imutran’s senior scientists and management entitled “ALL SURGERIES ARE ON HOLD UNTIL FURTHER NOTICE.” He explains: “Further to this email from ██████████, ALL THE SURGERIES HAVE BEEN PUT ON HOLD AS OF NOW.”¹⁹⁶ (original emphases) He continues:

“Indeed, animal welfare is our concern n.1 and this issue must be addressed as a matter of urgency in a meeting with ██████████ [one of the xenotransplant surgeons]. In this meeting, every single animal in the group will be analysed individually, with the aim of understanding:

1. what went wrong
2. what steps should be implemented to find an immediate remedy and prevent this from happening again...”

The concern expressed for animal welfare may seem slightly surprising given the severe suffering experienced by higher primates in the course of Imutran’s experiments and the persistence with biopsies. But, in the light of Imutran’s determination to reach the goals set them by Novartis, this concern may be a reflection of the desire to achieve longer survival times in order to progress towards clinical trials.

Six of the twenty monkeys used in this study¹⁹⁷ were part of the ill-fated consignment that had arrived in early August 1998, three of whom had died en route. Technical

¹⁹⁵ See Files CY24.1→CY24.3.

¹⁹⁶ See File ██████████

¹⁹⁷ A472f, A477m, A467m, A476f, A475m, A474f.

failures had been redefined to include deaths within four days of surgery:¹⁹⁸ there appears to have been eleven such failures in study IAN022, hence [REDACTED] reference to “over 50% TF’s.” **A172f** survived 19 days before she was euthanased due to a “persistently non-healing wound”¹⁹⁹ on her leg. Once again, it has been recorded that the biopsy procedure accounted for an animal’s life: **A169f** “survived for 17 days and suffered a respiratory arrest during sedation, prior to the biopsy procedure.”

As usual, the clinical signs record the demise of the animals. One monkey was found “in a state of collapse.” “Brown, clear vomit” was noted in **A345f**’s cage on day 8. She was also observed straining to urinate. Towards the end, the records state: “White frothy vomits on tray... Red staining noted on floor of cage... Loose/liquid faeces. Vomit... Reluctant to move. Loose/liquid faeces. Sedated and euthanased.”

A467m suffered a swollen abdomen and diarrhoea. Before he died on day 15, he was subdued and huddled on his perch, tremors in his limbs were noted together with swelling around his eyes and the wound in his abdomen. On the morning of **A475m**’s death after 9 days, he was seen lying on the cage floor with yellow discharge from his nose. **C107m** appears to have fairly active and occasionally aggressive for his first month, although he was salivating and may have been in discomfort after being dosed on day 20. Gradually he succumbed to diarrhoea towards the end of the month before he deteriorated, quiet and huddled with a swollen abdomen and, finally, “generalised piloerection” on his 35th and final day.

C111m’s scrotum and thighs appear to have been swollen throughout most of his 36 days. In his final few days, his tail was also swollen, and he became unsteady on his feet, with piloerection. His diarrhoea seems to have worsened until, in his closing 24 hours, it was yellow and green. **C105m** suffered similar symptoms, plus a swollen abdomen and eyelids, as well as more extensive vomiting. Finally, when he was killed after 30 days, his legs, abdomen, muzzle, arms and around his eyes had swelled up.

The decision to halt surgeries in the wake of the numerous technical failures in study IAN022 may have marked a pause in transplant experiments until early 2000. There were no transplants in the second half of 1999. The next reference to xenotransplant procedures appears in February 2000, again in connection with technical failures.²⁰⁰ On 3rd February, [REDACTED], Novartis’ [REDACTED], emailed fellow Novartis managers and senior staff at Imutran to tell them: “In view of the recent experimental failures and as discussed by phone with [REDACTED], I would like you to interrupt any further experiments until better understanding of the reason for these failures has been determined.”²⁰¹

¹⁹⁸ See File [REDACTED]

¹⁹⁹ See File CY23.3.

²⁰⁰ Home Office Minister Mike O’Brien MP’s written answer of 28 June 2000 confirms that these involved cynomolgus monkeys rather than baboons.

²⁰¹ See File [REDACTED]

6.6 Summary of Part III: cynomolgus monkeys in xenotransplantation research

Importation

Part III of this report has detailed the suffering endured by cynomolgus monkeys used in xenotransplantation research. At least 424 such higher primates have been imported from Mauritius, Indonesia and the Philippines for use in Imutran's research programme at HLS.

The international transport of animals severely compromises and endangers their welfare and lives. At least seven cynomolgus monkeys have died during importation to the UK for vivisection since 1995. Three of these seven were acquired from a breeder in the Philippines for use in Imutran's xenotransplantation research. On 5th August 1998 the animals were found dead at an airport outside Paris. They had spent 35 hours in crates measuring just 39cm x 24cm x 44cm. The eventual journey time to HLS' facility at [REDACTED] was approximately 48 hours. These containers broke International Air Transport Authority (IATA) regulations because:

1. they were too small for the animals to stand, turn and lie down in a natural manner;
2. they were only ventilated on two sides when the regulations stipulate ventilation on at least three sides.

Furthermore, evidence suggests that some of the females may have been in heat: IATA regulations advice against shipping females in heat because of the adverse effects it has on males being transported with them.

Apart from a temporary suspension of the supplier of the primates from the "approved lists" no action appears to have been taken by the Home Office in response to these regulatory breaches and subsequent deaths. Indeed, in listing the deaths of cynomolgus monkeys in transit in a Written Answer the department did not fully answer the question posed and disclose that these animals were destined for xenotransplantation research.

Intriguingly, Imutran attempted to remain anonymous throughout the investigations into the cause of the animals' deaths. This may have been in respect of MAFF rather than the Home Office, as the Home Office were fully aware of the context of the primates' deaths.

Vivisection

In excess of 424 cynomolgus monkeys were subjected to experiments that fall into six broad categories. 79 animals were killed in research into the xenotransplantation of:

1. **pancreatic islet cells from pig foetuses,**
2. **pig bone and pig cartilage.**

Neither of these research paths appear to have been subsequently pursued.

59 primates were used in **studies to test immunosuppressive techniques without xenotransplantation** procedures being performed upon them. An early developmental study transplanted the **hearts of cynomolgus monkeys into the necks of baboons**. A further 67+ monkeys were killed in studies that **transplanted piglet hearts into the abdomens of the primates** to investigate rejection – the monkeys' own hearts were left in place.

Technical failures were a particular problem with the porcine heart xenotransplantation procedures: in one study 33 out of 61 monkeys died within 24 hours of vivisection. Those who survived surgery were subject to a variety of distressing symptoms, including prolonged diarrhoea, a symptom of the gastrointestinal toxicity caused by the immunosuppressant drugs. Other malaises included nausea, vomiting, unsteadiness, gangrene, breathing difficulties, piloerection, passing blood in urine and faeces, salivation and swollen body parts including eyes, muzzle, abdomen and foreskin.

The main thrust of Imutran's vivisection of cynomolgus monkeys has been to study **renal xenotransplantation: the grafting of pig kidneys into primates**. Apparently, one of the reasons that this path was pursued in preference to a sustained effort at heart xenotransplantation was because Imutran/HRC thought that the Home Office would attempt to classify them as 'moderate' procedures rather than 'substantial'. The actual impact of the experiments on the animals, as evidenced by the recorded clinical signs and other pertinent documents, makes a 'moderate' classification of their severity hard to comprehend: a 'substantial' banding would appear to be far more appropriate.

Indeed, the records reveal a harrowing dossier of suffering. The initial studies often lead to the deaths of the primates because of fatal anaemia. This was a result of the inability of the pig kidney to produce the correct form of the hormone erythropoietin (EPO) which is required to stimulate the production of red blood cells in the bone marrow.

Renal failure itself, caused by rejection or other complications, caused the monkeys to be poisoned as their bodies failed to excrete waste products, including the highly toxic immunosuppressant drugs administered to the animals. The effects of renal failure include "nausea, vomiting, lethargy, drowsiness and eventually death." Taking these inevitable effects of renal failure into account, alongside the clinical records for the animals, makes attempts to classify these experiments as 'moderately' severe even more incredible.

The effects of subnormal kidney function coupled with high doses of immunosuppressants led to a number of horrific symptoms that are detailed in this chapter. The prolonged ordeal of some animals accentuates concern regarding the level of adherence to regulations during the course of these studies. Did these procedures involve breaches of the severity limit attached to their license, or was the severity limit set so high by the Home Office that the higher primates were exposed to quite severe suffering?

Indeed, these experiments and their devastating effects on the animals concerned raise the basic question: should these experiments have been permitted at all given UK legislation which states: "The Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated"? Article 8 of the European Directive 86/609 also applies: "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.**" (added emphasis).

Based on the evidence revealed through this report, we believe that the suffering inflicted on the primates in Imutran's vivisection programme at HLS is potentially in breach of both UK and European legislation. How the responsibility for such legal breaches, if confirmed through an independent judicial enquiry, is distributed between the Home Office, Imutran and HLS is not clear, although all these parties undoubtedly share moral responsibility for the ordeal of the animals.

Another significant theme to emerge is the catalogue of technical failures: monkeys who died as a result of complications with surgery. Their small size was one of the reasons for such failures. Other recorded causes include overdoses of anaesthetic, changes in the research personnel and irregular scheduling of vivisection procedures, a foreign body left inside a primate following surgery, and a kidney that froze between removal and transplantation. Despite the extensive experience gained by Imutran in these procedures, technical failures occurred at an alarming rate right up until the latest experiments. The 50%+ technical failure rate of one of the most recent studies, IAN022 – nicknamed the 'Full Monty' – forced Imutran management to suspend research in May 1999 and initiate an enquiry into the affair. This process was repeated in February 2000, this time with senior Novartis personnel involved.

The problems with the experiments did not stop there. Imutran were keen to perform regular biopsies on the xenografted kidneys in order to discover information about how the organs were rejected. These procedures killed at least three monkeys, leading some Imutran scientists to question the wisdom of persisting with the biopsies. However, these concerns were overruled because of Imutran's desire to achieve improvements in the survival times of the xenotransplants. The scientific usefulness of biopsies appears to be questionable given that one of the biopsies is reported as having shown a graft as normal whereas the post mortem revealed rejection. The issue of biopsies even appears to have created conflict with the Home Office, with Imutran reported by a Government advisor as having moved their research from the UK to Canada because of new restrictions enforced by the UK Government.

Yet another set of complications were revealed in the minutes of a pathology meeting held to review the outcome of one of the latest studies, IAN020. It emerges that a viral infection – cytomegalovirus (CMV) – became activated in several animals following surgery. It seemingly hastened their deaths, in some instances through inflammation of the kidney, lungs and digestive systems. With a severely impaired immune system, the virus was permitted to multiply with no effective restraint. In response, Imutran discussed the administration of anti-viral drugs. The issue of gastrointestinal toxicity arises, but the company felt that the anti-viral treatment would not add significantly to the already-prominent levels of diarrhoea in the transplanted primates.

Infection caused by protozoa also created problems. The emergence of infections amounts to a potential shortfall with respect to a basic principle of Good Laboratory Practice. This requires 'test systems' (i.e. the primates in these procedures) to be free of diseases and conditions that may affect the outcome of the study.

Furthermore, some of the monkeys developed an early form of lymph cancer. The cause of this disorder is unknown, though two possibilities have been suggested: the immunosuppressive drugs or a virus originating from the pigs.

The pathology findings themselves created problems for Imutran: two meetings generated conflicting diagnoses for some of the primates killed in study IAN020. Imutran admitted that these conflicts in data jeopardised their ISO 9000 status.

Despite the ordeal of hundreds of higher primates sacrificed for the sake of this technology, as well as thousands of genetically manipulated pigs, Imutran appear to have made no meaningful progress towards developing a successful xenotransplantation procedure in primates. The longest survival time revealed by the acquired documents - 78 days - occurred in 1997. No wonder an 18 month time limit to achieve a quantum leap in survival times was eventually set in early 2000, following discussions with Novartis senior management.²⁰²

²⁰² See File [REDACTED]

Index of filed documents accompanying Part III: Cynomolgus monkeys in xenotransplantation research

- CY1.1:** "Primate acquisition form" (internal Imutran document), 9 July 1996.
- CY2.1:** "Primate Acquisition", 10.7.96
- CY3.1:** "Primate Acquisition", 14.10.96.
- CY4.1:** Fax from [REDACTED] (Imutran) to [REDACTED] (HLS), 23.2.98.
- CY5.1→CY5.16:** Letter (with attachments) from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspectorate), 11 August 1998, "RE Delivery of 33 Cynomolgus Macaques on 6 August 1998."
- CY6.1:** Letter, [REDACTED] (Imutran) to [REDACTED], Home Office Inspector, 6.11.98.
- CY7.1 & CY7.2:** Fax, [REDACTED] (Imutran) to [REDACTED] (HLS), 19.11.98 .
- CY8.1→CY8.3:** Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspectorate), 22.1.99.
- CY9.1:** Fax from [REDACTED] to [REDACTED] (Imutran), 1.2.99
- CY10.1→CY10.3:** Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office Inspectorate), 10.5.99.
- CY11.1→CY11.3:** Study/Report Summary (estimated date, third quarter 1999)
- CY12.1→CY12.3:** Operating Protocol for Heterotopic Abdominal Heart Transplantation – Pig to Cynomolgus Monkey, [REDACTED], Imutran Surgeon. (No date: estimate late 1994/early 1995)
- CY13.1→CY13.11:** Imutran Draft planning document: Primate Trials of Transgenic Pig Organs: Phase Two, [REDACTED], 14.11.94.
- CY14.1 & CY14.2:** "Notes of the Meeting at HRC, 28 April 1995."
- CY15.1 & CY15.2:** "A review of pig to monkey kidney transplantation. Meeting held on 19th December 1995."
- CY16.1→CY16.7:** "Kidney Summary since Sept. 1"
- CY17.1→CY17.10:** Letter from [REDACTED]
[REDACTED]
[REDACTED] to [REDACTED], 11 June 1997. Plus accompanying document: MD Application, [REDACTED], Pig to primate renal xenotransplantation.
- CY18.1 & CY18.2:** Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office), 4 February 1998.
- CY19.1→CY19.3:** Letter from [REDACTED] (Imutran) to [REDACTED] (Home Office), 11 February 1998. Attached: surgery reports for February 1998 and summary of results of IAN009.
- CY20.1 & CY20.2:** "Progress Review Meeting Minutes". Meeting held 29 January 1999. Minutes generated 1st March 1999.
- CY21.1→CY21.6:** "Responses to Comments Raised by the Primate Sub-Committee" (estimated date – circa March 1999)
- CY22.1→CY22.3:** "Clin/Path Meeting Minutes". Date of meeting: 26th March 1999. Date of minutes: 12th April 1999.
- CY23.1→CY23.3:** "Clin/Path Meeting Minutes". Date of meeting: 23rd April 1999. Date of minutes: 26th April 1999.
- CY24.1→CY24.3:** "Progress Review Meeting Minutes". 30th March 1999.
- CY25.1:** [REDACTED]

PART IV

HUNTINGDON LIFE SCIENCES

CHAPTER 7

The conduct of xenotransplantation research at HLS

7.1 Huntingdon Life Sciences (HLS)

In an effort to investigate the potential success of xenotransplantation and subsequently gain approval from Government regulators²⁰³ to commence human trials, Cambridge-based biotechnology company *Imutran* commissioned *Huntingdon Life Sciences* (HLS) to conduct a substantial primate vivisection programme. HLS is an international contract research company, with UK establishments located near Huntingdon, Cambridgeshire and [REDACTED]. Its geographical proximity to Imutran and its extensive facilities for primate vivisection made it the obvious choice for this research.

Since 1994 HLS has staged approximately 50 separate primate xenotransplantation studies on behalf of Imutran.²⁰⁴ The documents upon which this report is based include study reports for 39 out of those 50. They reveal that at least 424 cynomolgus monkeys and 49 baboons (both higher primate species closely related to human beings) have been vivisected during the course of the project.

This extensive use of higher primates – the ‘cousins’ of human beings – in procedures that have caused severe suffering raises acute ethical concerns about this research programme. These concerns are intensified by the suffering and killing that 10,000 pigs – highly intelligent creatures who match dogs in terms of sensitivity and intelligence – have been subjected to in order to produce transgenic organs for research purposes.

On the other hand, the supposed benefits of xenotransplantation appear to be extremely speculative, not to say negative, given:

1. the predictably obstinate immunological and other biological barriers to such discordant xenografts that have prevented the development of transplantable porcine organs; and
2. the ineradicable danger of transferring novel infectious diseases into the human population which could trigger new pandemics.

In the context of grave doubts about the ethical and legal propriety of this research programme, the conduct of such research **at HLS** requires particularly close scrutiny because of previous incidents of animal abuse and breaches of the conditions of the

²⁰³ E.g. In the UK the relevant body is the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). In the USA, the central regulatory body is the federal Food and Drug Administration (FDA).

²⁰⁴ “Primate Transplantation: Data and Process Review” by [REDACTED] (Imutran), 13/02/00, page 3. [copy of document injunction]

establishment's Certificate of Designation – a Government-issued permit allowing it to carry out research on animals.²⁰⁵

The Countryside Undercover revelations: the Animals (Scientific Procedures) Act and accompanying regulations

The most serious problems to have emerged at HLS were revealed by a Channel Four documentary, entitled *It's a Dog's Life*, screened in March 1997 as part of the Countryside Undercover series. In response, Home Office Minister George Howarth MP stated: "We were extremely concerned about the events shown in the Channel 4 programme..."²⁰⁶ Inside the dog toxicology unit, beagles were shown being punched and slapped by HLS employees, two of whom were subsequently convicted under the Protection of Animals Act 1911. The Government's advisory body on animal experiments, the Animal Procedures Committee "unequivocally condemned the brutality that was shown in the film."²⁰⁷

Other failures relating to the care, treatment and handling of animals were discovered by a Home Office investigation, including the assignment to new staff of undetermined competence the job of checking the animals' health status.

The Home Office investigation also found that experimental data had been falsified. The Minister concerned also acknowledged that "the establishment was not appropriately staffed and that animals were not at all times provided with adequate care," leading to breaches of two of the standard conditions which apply to all Certificates of Designation.²⁰⁸

Subsequently, on 24 July 1997, the Home Secretary threatened to revoke HLS's Certificate of Designation – an unprecedented move.²⁰⁹ The revocation would have taken place immediately if not for the Government's apparent concern about the killing of thousands of animals kept at HLS at the time, as well as the potential job losses at the firm. The Government decreed that the retention of the Certificate was dependent upon the fulfilment of 16 wide-ranging conditions supposedly designed to rectify the problems identified at HLS and prevent their recurrence.²¹⁰ On 27 October 1997, the Government claimed that HLS had met the 16 conditions and had been issued with a new Certificate on 29 September 1997.²¹¹ Many observers in the animal protection movement were dubious about this course of events, particularly because of the tradition of unwarranted protection and support provided by the Home Office to

²⁰⁵ Mr George Howarth, Parliamentary Under-Secretary of State at the Home Office. House of Commons Hansard Written Answers for 24 July 1997, Columns: 678-680.

²⁰⁶ Mr George Howarth, Parliamentary Under-Secretary of State at the Home Office. House of Commons Hansard Written Answers for 24 July 1997, Column: 678.

²⁰⁷ **Report of the Animal Procedures Committee for 1997**. London: The Stationery Office: p.15.

²⁰⁸ Mr George Howarth, Parliamentary Under-Secretary of State at the Home Office. House of Commons Hansard Written Answers for 24 July 1997, Columns: 678-680.

²⁰⁹ **Report of the Animal Procedures Committee for 1997**. London: The Stationery Office: pp.15-16.

²¹⁰ **Report of the Animal Procedures Committee for 1997**. London: The Stationery Office: appendix D, pp. 24-25.

²¹¹ Mr George Howarth, Parliamentary Under-Secretary of State at the Home Office. House of Commons Hansard Written Answers for 27 October 1997, Columns: 743-745.

the vivisection industry, together with the lack of independent assessment of its investigative and decision-making procedures.

Countryside Undercover: Breaches of Good Laboratory Practice (GLP) at HLS

The welfare of animals was not the only area of serious concern regarding HLS' practices to emerge from the undercover investigation. International standards of GLP exist to which testing laboratories are obliged to adhere in order to maximise the reliability of data generated by the studies they conduct (see next section for more details about GLP). The Department of Health is the national authority in this country for monitoring standards of GLP.

Dr Gill Langley, a scientific adviser to animal protection organisations and now member of the Government's advisory committee on animal experiments, the Animal Procedures Committee (APC), submitted a report in April 1997 to the Department of Health. Her report made charges of serious violations of principles of GLP at HLS. These included incompetent drug injection and blood sampling; staff brutality, which could affect the outcome of the test (let alone causing animals to suffer); falsification of the weighing of test doses; falsification of weights of food consumed by dogs; and sloppy record-keeping.

The Department of Health's GLP Monitoring Authority (GLPMA) responded by slapping a Warning Notice on HLS on 1 May 1997. Following subsequent inspections at HLS, the GLPMA "found a number of serious deficiencies in their GLP procedures." The GLPMA also instructed HLS that some studies on dogs were, in their view, not compliant with GLP because of serious deviations from GLP procedures. HLS were ordered to admit this to the sponsors of these studies.²¹² Tragically, the sponsor ordered a repetition of the studies on the dogs.

The GLPMA stopped short of stripping HLS of its membership of the GLP programme: thus HLS escaped a potentially devastating blow to the company which would have prevented it from conducting studies intended for submission to regulatory authorities. By 15 July 1997, the GLPMA claimed that they were "satisfied with the changes in administration and management procedures and will not be removing them from the GLP programme at present," adding, "Their continuance in the GLP programme will depend upon a re-inspection in September 1997." Presumably HLS passed this re-inspection.

The documents upon which this report is based - which include study reports written by HLS, correspondence between HLS and Imutran, and internal Imutran documents - provide the first opportunity to assess independently the performance of HLS before, during and after the *It's a Dog's Life* affair. In particular, the new evidence enables us to answer a crucial question: Did HLS really put its house in order as the Home Office claimed and the GLPMA believed? We believe that the evidence indicates that this was not the case.

²¹² Letter from D F Moore (Dr) (UK GLPMA) to Dr Gill Langley, 29 July 1997.

7.2 Good Laboratory Practice (GLP)

In addition to the 16 Home Office conditions, HLS must comply with the general regulations governing Designated Establishments, included amongst which are rules relating to the care and housing of animals. Another crucial measure of HLS' performance, as referred to above, is its compliance with Good Laboratory Practice (GLP).

The Good Laboratory Practice Regulations (last updated 1999) are a Health and Safety Statutory Instrument (1999 No. 3106) administered by a Department of Health body known as the Good Laboratory Practice Monitoring Authority (GLPMA). GLP compliance is intended to ensure that data generated by studies of technologies and products is as reliable and valid as possible when submitted to the relevant regulatory authorities for approval. In order for studies intended for submission to regulatory authorities to be conducted at a particular site, the operator of that site must be a member, or "prospective" member of the UK GLP compliance programme, administered by the GLPMA. If a study is conducted at a test facility which is not a member of the UK GLP compliance programme, then the operator of that facility "shall be guilty of an offence."²¹³

In the case of xenotransplantation research, GLP compliance of studies and establishments has these fundamental objectives:

- to enable the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) and regulatory bodies in other countries to assess reliably applications to conduct human clinical trials of xenotransplantation procedures.
- to assist the Animals (Scientific Procedures) Inspectorate in assessing the merits of xenotransplantation project licence applications, based on the record of previous relevant "GLP compliant" studies presented in support of the application, and in the expectation that the data generated by the proposed animal research programme will be authentic and the claimed "benefits" are, thereby, realised. The Home Office demonstrated the importance of GLP compliance at HLS in the third of its 16 conditions: "That summary findings of the Department of Health Good Laboratory Practice scrutiny be disclosed by the establishment to the Home Office with confirmation that any process problems have been corrected."²¹⁴

An operator who is deemed by the GLPMA to be "not capable of ensuring that the principles of good laboratory practice are adhered to at those premises" is liable to be ejected from the UK GLP compliance programme, and thus forbidden from conducting further regulated studies.²¹⁵ The Warning Notice issued by the GLPMA to HLS on 1 May 1997 was a potential precursor to such an ejection.

²¹³ Regulation 4.

²¹⁴ **Report of the Animal Procedures Committee for 1997.** London: The Stationery Office, p. 24.

²¹⁵ Regulation 6, para. 3(b).

The principles of GLP apply to the “organisational structure surrounding the study” and to “the conditions under which the study is planned, performed, monitored, recorded, archived and reported.”²¹⁶ Some of the principles of GLP, listed in Schedule 1 of the GLP Regulations, that turn out to be relevant to this report on xenotransplantation research at HLS, include:

- Suitable facilities should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems. [Part III, 2(2). A *test system* in the context of xenotransplantation research refers to the primate recipients of pig organs.]
- Chemicals, reagents and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. [Part IV, 4.]
- Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in regulatory studies should be maintained. [Part VI, 1(1). A *test item* in this context refers to the transgenic pig organs and the immunosuppressive treatments.]
- Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the highest degree possible and contamination or mix-up are precluded. [Part VI, 1(2).]
- Storage containers should carry identification information, expiry date, and specific storage instructions. [Part VI, 1(3).]
- All data generated during the conduct of the regulatory study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated. [Part VIII, 3(3).]
- The final report should include all information and data required in the study plan. [Part IX, 2(f(ii)).]

A statement submitted to a regulatory authority detailing the level of adherence of a study to the principles of GLP is known as a GLP instrument. To claim falsely that a whole or part of study was performed in accordance with GLP principles, is to commit the offence of making a “false GLP instrument.”²¹⁷ Simply making, or having in one’s possession, a false GLP instrument with the intention of supplying it to a regulatory authority are also offences that render the guilty party liable to a maximum prison sentence of two years.

²¹⁶ Regulation 7, para. 1.

²¹⁷ Regulation 12, para. 4(b).

7.3 Early warnings: Imutran highlights “*fundamental shortfall in GLP compliance*” at HLS

[Throughout this section, relevant GLP principles that may have been breached are referred to in square brackets in a smaller font.]

Bad laboratory practice?

Two Imutran reports on the GLP status of the studies they had commissioned from HLS were produced in early 1996. In the first, dated 16 February 1996, [REDACTED], Imutran’s [REDACTED], looked at HLS’ compliance with study protocols, company Standard Operating Procedures (SOPs) and Good Laboratory Practice – all critically important areas.

In her report,²¹⁸ [REDACTED] concluded that the studies she reviewed (ITN/3, 4, 5 and 6) were not GLP compliant, although the protocols for the studies required such compliance.

[Each test facility management should ensure that the principles of good laboratory practice are complied with in its test facility. [Part 1, 1(1).]

One of the reasons she gave for why she believed “that these studies have, in fact, not achieved full GLP compliance,” was this:

"Changes in study design are currently documented using retrospective protocol amendments. Retrospective amendments are not acceptable to DoH [administrators of the GLPMA] as evidence of changes approved and authorised by the Study Director and Sponsor and communicated to study personnel prior to the events."

[As respects the study plan – deviations from it should be described, explained, acknowledged and dated in a timely fashion by the study director and/or any principal investigators and maintained with the raw study data. [Part VIII, 1 (2(b)).]

Another factor leading her to conclude that the studies were not GLP compliant was as follows:

"There are no data held by HLS to support the surgery sections of the protocol, other than an anaesthetic record, although certain records may have been maintained by the surgeons... Thus currently it appears that there are no data to indicate how surgery was performed, what organs were involved, which personnel were involved, whether these staff were adequately trained and experienced etc. Since the purpose of the study is to monitor the robustness of the xenotransplant, the lack of documentation of the procedures employed and personnel involved is a *fundamental deficiency*." [my emphasis]

[The study director should ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; and acknowledge

²¹⁸ See files at HLSAPP1.

deviations from standard operating procedures during the conduct of the study. [Part I, 2(2(e)).]

The study director should ensure that all raw data generated are fully documented and recorded. [Part I, 2(2(f)).]

All study personnel are responsible for recording raw data promptly and accurately and in compliance with these principles of good laboratory practice, and are responsible for the quality of their data. [Part I, 4(3).]

██████ went on to comment: "The surgeons involved with these studies have maintained some records of transplantation which it may be possible to use in support of operations performed without data recording at HLS." But the surgeons' records, she added, "have not yet been assessed by Imutran QA." To what extent Imutran were able to retrieve the situation when it came to writing their final GLP submission is not clear. But the failure on the part of HLS, as claimed by ██████, remains.

Other problems noted in her inspection included:

- "It is not acceptable for unlabelled medication to be administered to study animals. At least the identity of the substance, its batch number and expiry date plus storage conditions should be added to the bottles to enable the doser to assure himself that he is giving the appropriate substance and that it is fit for use." This is extremely important where very powerful compounds such as ██████ are being used. If administered at the wrong dose, they may either permit or accelerate xenograft rejection, or cause kidney failure. Apart from ruining the experiment, the effects on the animal concerned could be devastating. There were other concerns highlighted by ██████, some of which also contributed to the possibility of mis-dosing. They included:
- Uncovered veterinary medications stored next to test drugs used in the experiment.
- Unsatisfactory preparation and labelling of each animal's drug dose.

[Chemicals, reagents and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. [Part IV, 4.]]

[Storage containers should carry identification information, expiry date, and specific storage instructions. [Part VI, 1(3).]]

- Old, inaccurate and unauthorised instructions.
- Unsatisfactory "housekeeping".
- Persistently inadequate humidity leading to breach of protocol in the baboons' environment.

[The regulatory study should be conducted in accordance with the study plan. [Part VIII 3(2).]]

Later in February 1996, Imutran's [REDACTED], an animal technician who was later to assume overall responsibility for coordinating the company's primate vivisection programme, completed another report into GLP compliance of HLS studies.²¹⁹ [REDACTED] had reviewed protocols for studies ITN1-8, conducted interviews and reviewed all surgery records for ITN3, 4 and 5. This was his startling conclusion:

"In summary the project identified a *fundamental shortfall in GLP compliance* for the historical studies... I believe this was a result of a clash of cultures between Imutran staff, and staff at HLS who are more familiar with the regimented nature of traditional contract toxicology. The very nature of the research carried out by Imutran requires that a contractor be extremely flexible, proactive and innovative, thus far I feel that *HLS have singularly failed to exhibit these attributes*." (my emphasis)

[Each test facility management should ensure that the principles of good laboratory practice are complied with in its test facility. [Part 1, 1(1).]]

[REDACTED] findings echoed those of [REDACTED], contradicting HLS's claims in their draft report of GLP compliance for studies ITN/3, 4 and 5. [REDACTED] went on to identify urgent action to be undertaken to salvage GLP compliance for the ongoing studies ITN/6, 7 and 8.

To understand what options Imutan had for seeking to retrieve GLP compliance before the final reports to the GLP administrative body had to be submitted, it is important to appreciate how advanced the various studies were when [REDACTED] and [REDACTED] wrote their reports.

[REDACTED] submitted her findings on February 16, 1996 - [REDACTED] 11 days later on February 27. A great many of the transplant operations for studies ITN1 through to ITN8 were already completed by then and the animals were dead. Here is the chronological breakdown:

For **ITN3**, the last (61st) monkey had been killed on 11 January 1996. **ITN 4** had run from July 1995 through to May 1996, with 19 of the 22 transplant procedures having taken place by the time of [REDACTED] February 27 report. The last procedures in study **ITN5** were conducted on 1st February 1996.²²⁰

ITN 6, 7 and 8 were said to be ongoing at the time of [REDACTED] investigation. However, in **ITN7** all four cynomolgus monkeys who underwent heterotopic cardiac xenotransplantation in this intended *long-term survival* study had died within one day of the procedures. These took place on 15th, 16th and 22nd January 1996. Additionally, two out of the three procedures in ITN 6 had also

²¹⁹ See files at HLSAPP2

²²⁰ ITN1 and 2 were "developmental" studies for which GLP compliance was not claimed and thus they were not a focus of attention for [REDACTED]'s project.

been completed by the time of [REDACTED] report (Surgery dates were 15/1/96, 5/2/96 and 4/3/96).

[REDACTED] had identified "a fundamental shortfall in GLP compliance" with respect to what he called the "historical studies" - probably a reference to ITN3, 4 and 5. He repeated [REDACTED]'s concerns about these studies and declared: "Major problems with surgery records, final reports should be produced but the detail of the wording of the final reports needs to be agreed between Imutran and HLS."

Most tellingly, his summary contains the following admission: "There is a chasm that needs to be bridged rapidly if future Imutran studies are to be compliant with GLP." The urgent "tactical remedial actions" he called for included:

- the improvement of surgery records to comply with GLP.
- "Blood sample/Tissue request forms to be produced. ([REDACTED] indicates that this has been implemented.)
- HLS staff to become proactive during the conduct of ITN studies.
- Necropsy/Pathology procedures to be reviewed.
- Patient medical histories to be produced."

As to reasons for the GLP shortcomings to date, [REDACTED]'s report offers this swingeing critique (already quoted above):

"I believe this was a result of a clash of cultures between Imutran staff, and staff at HLS who are more familiar with the regimented nature of traditional contract toxicology. The very nature of the research carried out by Imutran requires that a contractor be extremely flexible, proactive and innovative, thus far I feel that HLS have singularly failed to exhibit these attributes."

In addition to jeopardising the GLP status of the studies at HLS, these critical observations made by Imutran call into question the decision by the Home Office to licence this programme of research at HLS. This is because one of the factors that should be taken into account when the Home Office deliberates on a project licence application is "whether the facilities at the establishment are adequate for the scientific procedures."²²¹

Recording of GLP compliance

GLP compliance statements form part of a much larger document that records the progress and conduct of each of the 50 xenotransplantation projects. The complete document is known as a study report.

²²¹ Guidance on the Operation of the Animals (Scientific Procedures) Act 1986, London: HMSO (1990), p.13.

In the final draft study report for ITN3, there is no suggestion in the compliance statement of any deviations from GLP.

Elsewhere, however, there is a reference to problems with surgery records. File Note 4 tells us that in certain cases there was no recording of the times for "landmark" surgical procedures. Estimates had to be made based on the timings recorded for other procedures. The study director claimed that these other timings can be used as a general guide "because they *usually* only differed by about five minutes from the landmark procedure." [my emphasis]

Again, in the draft final report for ITN4, the GLP statement is devoid of any suggestion of GLP non-compliance. The report's File Note 5 does, however, contain an interesting admission: "Surgery Record Forms were only used for animals W151 and T407, as this form was only introduced during this study." However, an additional animal was vivisected after the introduction of these forms, which therefore do not appear to have been used for this animal.

The GLP compliance statement in the final draft study report for ITN5 also contains no mention of exceptions to GLP.

In the light of the above, it's worth recalling that [REDACTED] and [REDACTED] were of the opinion that studies ITN3, 4 and 5 had "in fact, not achieved full GLP compliance" ([REDACTED]) and had "a fundamental shortfall in GLP compliance" ([REDACTED]). Both authors drew particular attention to "major" problems with surgery records held by HLS - "a fundamental deficiency", as [REDACTED] described it.

[REDACTED]'s February 27 document provided no suggestions as to how GLP compliance could be salvaged for these by-then completed studies. Presumably this was because it would have been necessary to turn the clock back in order to rectify the "fundamental shortfall in GLP compliance." Hopes of achieving GLP compliance were reserved for future studies (ITN 6, 7 and 8). But even with these, [REDACTED] wrote of the "chasm that needs to be bridged rapidly" if this was to be achieved.

At this point, it is important to bear in mind the distinction between **final draft reports** and **final reports**. The study reports that have become available are in electronic format and are considered by the Study Director to be the **final drafts** of the study reports. These were at various stages of review (see below) before a final report would be issued by HLS to Imutran. Some hard copies of final reports issued by HLS to Imutran have become available, but these final reports do not correspond to the studies in question here. However, judging by the dates of these final reports issued by HLS (February-March 2000), final reports probably do exist for the studies in question here (ITN3→ITN8).

The final draft reports for these studies were at differing stages of review by HLS' Quality Assurance Department (QA) and the sponsor, Imutran. It is important to acknowledge that they are drafts and, therefore, it is possible that any deficiencies in GLP compliance that were not mentioned in these drafts may have been noted in the final reports. However, it is worth noting that the final drafts had been considered and submitted by the Study Director, [REDACTED], between 30 June 1998 and 6 October 1999 – two to three years after the studies were actually conducted.

██████████ had been on the list of recipients of ██████████'s report and had been interviewed by ██████████ and involved in the tactical remedial actions, according to his report. Thus it would appear that he would have been aware of the problems Imutran claimed existed with the studies.) Some drafts appear to have gone further through the review process:

- The 'draft' for ITN4 actually includes dates for the completion of the final report by HLS – 20 and 21 January 2000 – but remains unsigned and officially in draft format.
- A note at the beginning of the draft report for ITN6, dated 6 October 1999, states that it has already been audited by HLS QA.
- The QA statement for ITN7 says that audit findings were reported to the Study Director and management on 21 April 1998. *Presumably*, the draft report reflects the input from HLS QA, though this is not acknowledged by the Study Director's note at the beginning of the report.

Our main concern in this area centres upon the question of whether the final reports would accurately reflect the actual level of GLP compliance achieved by these studies.

We conclude that the acquired documents suggest that there is a case to answer regarding possible failures in GLP compliance and the faithfulness of the recording of the extent of GLP compliance in the study reports. We believe that there is sufficient evidence to justify an investigation into the possibility of such breaches of GLP Regulations as part of an independent judicial enquiry into the issues raised by this report.

Other errors

Other errors were occurring during study ITN4 that do not seem to have been picked up by ██████████. The description of the "Experimental Procedure" in the study report explains that during the necropsy "the xenograft was carefully removed and weighed." However, Appendix 10 to the report reveals that the weights of six of the xenografted kidneys were "not recorded in error." The difference in xenografted kidney weight between the times of transplant and death can help identify the cause of death and the extent and type of xenograft rejection. In fact the original protocol did not call for the weighing of the kidney at necropsy. But a subsequent amendment, signed and dated by the Study Director ██████████ on 18 August 1995 introduced this requirement.

[All study personnel are responsible for recording raw data promptly and accurately and in compliance with these principles of good laboratory practice, and are responsible for the quality of their data. [Part I, 4(3).]

All data generated during the conduct of the regulatory study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated. [Part VIII, 3(3).]

The final report should include all information and data required in the study plan. [Part IX, 2(f(ii)).]

The regulatory study should be conducted in accordance with the study plan. [Part VIII 3(2).]]

Furthermore, the study protocol for ITN 4 stated that the weights of "donor" transgenic piglets was "expected to be in the range 2 - 3 kg." (p.85) In reality, the weights of only two of the 22 "donor" piglets fell within this range, with the average weight being in the region of 5.7 kg (p.36 and the largest piglet weighing in at 10.7 kg.). This is a fairly drastic departure from the expectation stated in the protocol, but it is not mentioned in either the File Notes or under the "Deviations from Protocol".

[As respects the study plan – deviations from it should be described, explained, acknowledged and dated in a timely fashion by the study director and/or any principal investigators and maintained with the raw study data. [Part VIII, 1 (2(b)).]]

Culpability for GLP compliance failures may not be restricted to HLS, according to Imutran's own reading of the situation. For despite the main thrust of [REDACTED]'s criticism being directed at HLS, he also noted in his February 27 report that "Imutran staff have been allowed to conduct themselves as they see fit, when working at HLS."

Meanwhile...

The true and immediate significance of any failures in GLP compliance and other errors becomes clear when the relevant studies are analysed with regard to their impact on the animal 'models'. One hundred and twenty cynomolgus monkeys and an unknown number of pigs were vivisected during the course of studies ITN 3, 4 and 5. Hearts, kidneys and pancreatic islet cells removed from pigs were transplanted into these monkeys. Forty monkeys died as a direct result of the surgical procedure – these are termed "technical failures." Monkeys who survived the operation were administered high doses of immunosuppressants. Some monkeys were found dead in their cages, and others suffered clinical signs such as:

X34f: Swollen stomach wound seeping blood (ITN 5)

X51m: Quiet and huddled. Liquid faeces. Vomit in cage. (ITN 5)²²²

W763m: Very quiet and huddled. Swelling around both eyes. (ITN 3)²²³

Given the undeniably intense suffering endured by animals in these studies, a huge responsibility falls upon the researchers, at the very least, to follow procedures that ensure the integrity of the data generated.

²²² See File 992431.a8a

²²³ See File 971993.ap9

7.4 Imutran consider taking project away from HLS due to lack of confidence in the quality of work

“Recently uncovered ... problems” with GLP compliance and doubts about the long-term ability of HLS to conduct Imutran’s studies to a satisfactory standard led Imutran to examine other possibilities for the primate xenotransplantation programme. In his February 27 1996 report, [REDACTED] had compared the working methods of the two companies:

“Imutran is staffed with highly motivated individuals whose research predisposes them to be very flexible, innovative and extremely focused on their particular area of expertise. I also found that resource at Imutran is currently stretched such that researchers are having to undertake duties that detract from their primary role.

“HLS has a very regimented approach to the conduct of studies and are comfortable with programmes of work that can be planned well in advance and that stick fairly rigidly to a schedule.”

In a secret internal document dated 24 April 1996,²²⁴ [REDACTED] now discusses remedial options open to his company, while suggesting that attempts by Imutran to improve the situation “will not provoke, within HLS, the degree of flexibility required by Imutran.” Continuing to place work at HLS would mean that Imutran would have to **“accept that the service from HLS will fall short of their expectations”**.

The substantial financial burden of contracting work to HLS (£1,000,000 up to this date) further emphasised the need to review all possible options. For example, [REDACTED] refers to what he regarded as a rather hefty mark-up demanded by HLS for some services: “We are aware that HLS charge Imutran £3,000 for each cynomolgus monkey that they import on our behalf. The purchase price of the animals is actually closer to £1,500 (An actual quote was £1,200)...”

One option mentioned was re-locating the work at [REDACTED] in [REDACTED] - though the geographical distance from Cambridge ruled this out. [REDACTED]’s memo also examined in detail the logistics of hiring and modifying an existing HLS facility at [REDACTED] and staffing it directly with Imutran employees. Taking such a course would mean that “the quality of the work performed will be directly under Imutran control and the flexibility and responsiveness, currently lacking with HLS will be achieved.” Despite the apparent enthusiasm for this option it does not appear to have been pursued.

An example of HLS’s inability to fulfil Imutran’s requirements is revealed in a fax from the commissioning company to [REDACTED], the Study Director for Imutran Studies at HLS.²²⁵ It was dated 23 October 1996 and entitled “LATE ARRIVAL OF BLOOD SAMPLES”. An exasperated [REDACTED] complains:

²²⁴ See files at [REDACTED]

²²⁵ See file HLSAPP4A.1

“The situation continues to frustrate our laboratory staff. Weekday arrival times since October 7th have not improved since we last spoke about this topic. From 12 deliveries we have received samples at 10.00am ONCE!” (original emphasis)

7.5 Countryside Undercover, ‘It’s a dog’s life’: Did HLS really satisfy the 16 conditions?

This question is one of the most politically sensitive to be raised by the acquired information. If HLS did not satisfy the 16 conditions specified by the Home Office – despite public assurances to the contrary - then we are left with three likely explanations:

- The Home Secretary misinformed the House of Commons and the public by claiming that HLS had satisfied the 16 conditions.
- The Animals (Scientific Procedures) Inspectorate misinformed the Home Secretary about the situation at HLS.
- HLS misinformed the Animal (Scientific Procedures) Inspectorate about the implementation of the required improvements at their establishments.

Breach of the law: Unauthorised re-use of animals at HLS

A report by Imutran’s ██████, dated 13 January 1998,²²⁶ is particularly damaging to the notion that the 16 conditions had been satisfied. It shows that within six weeks of HLS being issued with a new Certificate, a failure had occurred that proper adherence to the conditions should have been prevented.

█████’s report relates to a group of cynomolgus monkeys who had already been part of a previous experiment and were now being “re-used” in another one, without prior Home Office approval. This was a clear breach of the 1986 Animals (Scientific Procedures) Act, as ██████’s report explicitly acknowledges. The re-use occurred on 6 and 7 November 1997 when the monkeys were dosed with the hormone ██████²²⁷ prior to scheduled xenotransplantation experiments. Their previous use had been as part of a ‘control group’ in an aborted toxicology (chemical testing) study. ██████’s report does not describe exactly what kind of procedures the monkeys had initially been subjected to or what the welfare impact of the re-use was. But the important aspect of this affair was that there had been a procedural breakdown and a consequent breach of the law: if no additional insult to the animals’ welfare occurred, this would have been due more to luck than judgement.

²²⁶ See files at HLSAPP5A

²²⁷ ██████ is a hormone administered to primate recipients of pig kidney xenografts. ██████ is produced in primate kidneys and stimulates the production of red blood cells in the bone marrow. However, pig kidneys fail to produce ██████ when transplanted into primates, resulting in fatal anaemia.

█████'s report sought to reveal the history of the debacle. He traces it to a joint HLS-Imutran progress review meeting on 16 October 1997 at which Imutran staff identified a group of cynomolgus monkeys "ideally suited for surgical use" due to their weight. According to the minutes of that October meeting, a HLS manager, █████ (who is said to have been present on 16 October) was delegated with the task of providing Imutran with "Details of previous use of these animals... so that relevant selection can be made." This task does not appear to have been carried out, notwithstanding the fact that minutes of the meeting were also faxed to HLS with a written request that they be circulated to relevant staff. It seems there was no such circulation. The reason, according to HLS? The fax did not transmit completely.

Imutran subsequently instructed HLS to begin dosing the monkeys with █████ – a re-use spotted two days after dosing commenced when a HLS technician who was familiar with the animals arrived for work. When the Home Office Inspectorate was informed of the incident two days later, the official concerned is said to have suspended immediately the entire research project pending the outcome of his investigation. At the time of █████'s 13 January 1998 written inquest, the Inspector's report had not been published.

In fact █████'s 13 January document contains another insight into the peculiar tensions that were afflicting the two companies over the re-use debacle. On 11 November, █████ and another member of HLS staff, █████, were prepared to "confirm that *the error lay within HLS* and no Imutran staff are at fault". The following day, █████ faxed █████ to thank him for coming clean. █████ comments:

"It is clear from what you said that any remedial actions that may be required lay within HLS, and were not the result of an error here at Imutran."

Two days later, a pair of senior managers at HLS telephoned █████, who records that they "angrily denied any liability within HLS." The pair was █████ and █████ – the latter, according to the minutes of the 16 October meeting, having been told to check whether the group of candidate monkeys had been previously used.

One of the most disturbing aspects of this incident is its timing - just over one month after HLS had been given a clean bill of health by the government minister concerned. In a written answer on 27 October 1997, George Howarth, then Parliamentary Under-Secretary at the Home Office, told Parliament that HLS had satisfied the 16 conditions set by the Home Secretary Jack Straw "to prevent any recurrence of the events shown in the television programme."²²⁸ The fifth condition had stated:

"That adequate provision has been made for regular and effective means of communication between those entrusted with responsibilities under the Act."

The re-use incident demonstrates that serious breakdowns in communication were still taking place, leading to further breaches of the A(SP)A.

²²⁸ Mr George Howarth, Parliamentary Under-Secretary of State at the Home Office. House of Commons Hansard Written Answers for 24 July 1997 and 27 October, Columns: 678-680 and 743-745 respectively.

‘Freezing’ of project licence

Earlier in this section, reference was made to the Home Office Inspector’s suspension of the entire research project pending the results of his investigation into the re-use of animals. According to ██████’s report, the suspension took place on 10 November 1997, and it was Project Licence PPL 80/848 that was immediately frozen. ██████’s report is dated 13 January 1998, at which point the results of the Inspector’s investigation were still awaited. Even so, the acquired study reports reveal that just seven days after the ‘total freeze’ and at least two months before the inspector formally reported, experiments were again being conducted under the project licence concerned. Study **IAN 007/984690** involved the transplantation of pig hearts into baboons on 17 November, 9 December 1997 and 5 January 1998. In study **IAN005-985228** - conducted under the same project licence - two monkeys, whose spleens had been removed, were given pig kidneys on 2 December 1997. And four animals were still alive and continued to be dosed with immunosuppressants at the time of and immediately after the ‘freeze’ of the Project Licence.

The speedy manner in which HLS returned to conducting transplant experiments raises further important questions about the way in which this incident was handled by all the parties concerned.

Conduct of studies during and shortly after threat to revoke HLS’s Certificate

Analysis of the final draft reports on five studies - which took place during and after the period when the Home Office was threatening to revoke HLS’s licence - reveals a catalogue of errors that potentially undermined compliance with Good Laboratory Practice. The third of the 16 conditions set by the Home Secretary was fundamental to the GLP question. It had demanded:

“That summary findings of the Department of Health Good Laboratory Practice scrutiny be disclosed by the establishment to the Home Office *with confirmation that any process problems have been corrected.*” (my emphasis)

Study IAN/001

Study IAN/001 involved the heterotopic²²⁹ transplantation of transgenic pig kidneys into 17 cynomolgus monkeys, eight of whom had been splenectomised (i.e. their spleens were removed) to further impair their immune systems. This study took place virtually entirely during the period when HLS’s Certificate of Designation was under threat - the first transplant occurring on 10 July 1997 and the last on 20 August 1997. The final monkey died on 2 October 1997.

²²⁹ “Heterotopic” means positioned in a different place to the normal position for the organ. This may or may not involve the removal of the ‘native’ organs. In these experiments, heterotopic renal xenograft studies usually involved the removal of the monkeys’ kidneys. On the other hand, in heterotopic cardiac xenograft experiments the baboons or cynomolgus monkeys’ hearts remained in place

The File Notes attached to the final draft study report detail deviations from the study plan that occurred during the course of this study.

[All data generated during the conduct of the regulatory study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated. [Part VIII, 3(3).]

The final report should include all information and data required in the study plan. [Part IX, 2(f(ii)).]

The regulatory study should be conducted in accordance with the study plan. [Part VIII 3(2).]

While some deviations are relatively minor and would not undermine data integrity, others are potentially more serious. As previously mentioned, in February 1996 Imutran had identified a “fundamental shortfall in GLP compliance” at HLS, particularly in the area of surgery records. However, in the final draft report on Study IAN/001, the File Notes 4, 5 & 7 indicate that problems were persisting more than 16 months later – a time when HLS should have been especially alert, given their obligation to fulfil the 16 Home Office conditions.

File Note 4 for Study IAN/001 relates to incomplete anaesthetic management forms, on which the weights of the source pigs and the primate recipients should have been detailed. More serious was the **failure to record the weight of the pig kidney at the time of transplant** for 12 of the 17 surgeries. This omission is important because the difference between the weight of the organ when grafted and its weight when removed from the recipient after death can be used to help calculate the type and extent of graft rejection – obtaining this knowledge being the fundamental object of the study. It is noteworthy that the Study Director did not attempt to dismiss the potential impact of this failure on the integrity of the study, a practice common in other File Notes.

File Note 5 for Study IAN/001 acknowledges that, in all but one procedure, the **finish time for surgery** has not been documented. The Study Director claims that a good approximation of these finish times can be estimated from other records.

File Note 6 refers to a **failure to make a complete record regarding the dose of a test substance** that the animals were receiving. The Study Director claims that all details were not recorded because the rules didn’t require it. “[T]he animals did not receive treatment with either a test substance or control article, based on the strictest definition of these terms,” he explained. The GLP regulations, however, describe a test substance simply as an item undergoing regulatory tests. It is true that the substances being tested at HLS (immunosuppressants) were already in use in human-to-human transplant procedures and so had already undergone regulatory trials, but they were now being tested in a novel setting and in novel formulations. As the Introduction to the IAN/001 study report states:

“The objective of this study, performed at Huntingdon Life Sciences Ltd, Huntingdon, England, was to investigate the effectiveness of immunosuppressive treatment on long-term renal xenograft survival in cynomolgus monkeys (*Macaca fascicularis*).” (page 8)

Furthermore, pages 10 to 12 of this final draft report contain a section entitled “**Test Substances**”, in which is [REDACTED] immunosuppressants: [REDACTED]. A reasonable interpretation is that the animals were indeed being administered test substances, and that the Study Director’s excuse is based on narrow semantics.

File Note 8 in the final draft of study report IAN/001 describes how records for **fluid intake, urine output and the administration of treatments** were not completed satisfactorily:

“[F]orms were partially completed by the technicians in advance, to act as an ‘aide memoir’ so that technicians attending the animals later in the day would be aware of which treatments/supplements were required to be administered. On review of the data it was found that some entries were not signed/time completed and it was not possible to verify in retrospect if the treatment had not been given or that the records had simply not been completed.”

[The study director should ensure that all raw data generated are fully documented and recorded. [Part I, 2(2(f)).]

All study personnel are responsible for recording raw data promptly and accurately and in compliance with these principles of good laboratory practice, and are responsible for the quality of their data. [Part I, 4(3).]

Appendix 6 of the study report reveals that this occurred on five occasions. The note also mentions that urine output from transplanted animals was impossible to measure when the animals were paired up with other monkeys in an effort to improve their survival times.

These omissions would seem to be fundamental deviations from the study plan in the context of renal xenograft experiments because, as the final draft of the Study Report itself states:

“Fluid consumption and urinary output were reviewed at regular intervals each day to determine how the transplanted kidney was functioning.” (25)

The Study Director makes no claim that these mistakes are insignificant with respect to the integrity of the study.

Additionally, the animals’ **food consumption** was “not recorded in error” on eight occasions. This is also a significant error because, as the report states: “[s]igns of xenograft rejection were manifest by falling urine output, rising creatinine, listlessness and *anorexia*.” (31, my emphasis) One of the reasons for a failure to eat could be intense and prolonged nausea resulting from renal failure or from poisoning due to the administration of heavy doses of immunosuppressant drugs.²³⁰ The presence of anorexia could prompt an attending veterinary surgeon to order an animal to be put down. Food consumption, for these reasons, is a crucial indicator in the experiments.

²³⁰ See file HLSAPP5B.2

In the course of this single study, there were 39 occasions when data, relating to fluid and food consumption and to urinary output, was “not recorded in error.”²³¹

A further error admitted in the final draft study report for IAN001 is as follows: “**Chemical analysis of formulated materials** to demonstrate achieved concentrations and determination of homogeneity and stability were not undertaken.”

This omission, which is recorded in the section of the report entitled “Compliance with Good Laboratory Practice Standards” (p.4), appears to be in contravention of these GLP Regulations:

[Handling, sampling and storage procedures should be identified in order that homogeneity and stability are assured to the highest degree possible and contamination or mix-up are precluded. [Part VI, 1(2).]]

If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. [Part VI, 2(5).]]

Page 16 of the final draft study report details how the immunosuppressant treatments were formulated, and reiterates the failure to take samples so that analysis could be undertaken into the concentration, homogeneity and stability of the drugs being used.

Given that the object of the study was “to investigate the effectiveness of immunosuppressive treatment on long-term renal xenograft survival in cynomolgus monkeys (*Macaca fascicularis*),” this would seem to be a fundamental omission.

Study IAN002

This study entitled **HETEROTOPIC RENAL XENOGRAFT TRANSPLANTATION IN CYNOMOLGUS MONKEYS WITH SPLENECTOMY** made use of five monkeys and ran from 30 September 1997 (the day after HLS was issued with a new Certificate by the Home Office) until 30 October 1997. Four of the monkeys died within 24 hours of surgery. The other survived 30 days.

Shortcomings in the conduct of this study were of a similar nature to study IAN001:

- Four out of the five transplanted kidneys were not weighed at the time of transplant.
- The finish times for surgery were not documented.
- Dose levels were not recorded on the clinical signs sheet, with the same justification given as for IAN001.
- The same fluid intake and urine output recording failures occurred.

²³¹ This figure omits the occasions when accurate data recording was not possible due to animals being paired up for part of the day.

- The immunosuppressant treatment formulations were not analysed in order to ascertain the achievement of required concentrations, homogeneity and stability.

Study IAN004

This kidney xenograft study investigated the effectiveness of a relatively low-level immunosuppressant regime comprising [REDACTED] and [REDACTED]. All six monkeys died within seven days.

These are the errors, some by now familiar, noted in the final draft study report:

- Some records, indicating which primate received which kidney, were incomplete.
- Two finish times for surgery “not recorded in error”.
- The discarding of dose residues has not been consistently reported. The Study Director admits that this is a deviation from Standard Operating Procedures, but claims that he is confident that the residues were, in fact, discarded and that fresh doses were made up daily.
- Food consumption for the last surviving monkey “not recorded in error” on one day.
- Three out of five “donor” kidney weights “not recorded in theatre in error”.
- Recurring errors in procedures for recording fluid intake and urine output.

Study IAN005

This was a “control” study that took place during November and December 1997 and involved kidneys from non-genetically modified pigs being grafted into cynomolgus monkeys. The most significant errors and deviations from protocol are as follows:

- Three operation times and two ischaemia times “not recorded in error”. Ischaemia, in this context, refers to the deliberate cessation of blood supply – during the course of an operation - to the organ that’s being transplanted. That ischaemia times are seen as particularly relevant can be judged from the fact that in subsequent studies (e.g. IAN020) ischaemia times were varied in order to investigate how this would affect the survival time for the xenograft.
- One of the pig kidneys was not weighed at the time of surgery.
- Daily food consumption measurements were not taken on two occasions.
- Records for the discarding of dose residues are again “generally incomplete”.

- Errors in the recording of fluid intake and urine output.
- Frequent deviations from protocol in the maintenance of temperature and relative humidity.

Despite these errors and omissions, in the final draft report, the Study Director claims that

“The study described in this report was conducted in compliance with ... Good Laboratory Practice standards and I consider the data generated to be valid”.

Study IAN007

Entitled “ORTHOTOPIC²³² CARDIAC XENOGRAFT TRANSPLANTATION IN BABOONS (WITH [REDACTED])”, this study used six baboons who were transplanted between 17 November 1997 and 23 March 1998. Mistakes and omissions included:

- One ischaemia time “not recorded in error”.
- Daily food consumption values “not recorded in error” on seven occasions.
- Fluid intake and urine output “not recorded” on 21 occasions. Although these values may seem less significant where cardiac xenografts rather than renal xenografts are being carried out, the information is still important to record because of the potential impairment to kidney function caused by the immunosuppressant treatments used in the study (e.g. [REDACTED]²³³).
- The times for the collection and disposal of doses were “on many occasions” not recorded, as is required by the relevant SOPs.
- Anaesthetic Management and Surgery record forms are incomplete.

7.6 Summary of routine errors and omissions at HLS in the course of xenotransplantation research

From the 39 final draft study reports that have been acquired (out of a total of approximately 50 studies) **520 separate data recording errors and failures** have been identified. In arriving at this figure, we have tried to exclude readings that were not recorded because the protocol did not require them to be (e.g. IAN007 included 29 unrecorded biochemistry readings for magnesium serum levels which were not demanded by the protocol until 20 March 1998, some three-quarters of the way

²³² “Orthotopic” means positioned in the normal place for the organ. This would necessitate the removal of the ‘native’ organ

²³³ ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1998-99, pp 854-856.

through the study); or because the protocol stated that they were only to be investigated at the discretion of the attending researchers and veterinarians.

After 24 July 1997, the date HLS were ordered to comply with 16 specific conditions or else lose their Certificate of Designation, we estimate that 186 errors occurred during the course of 17 studies. Four of the 17 were comparatively straightforward dosing studies involving 43 cynomolgus monkeys; no errors were recorded in regard to their conduct. The remaining 13 xenograft experiments killed 147 animals, the final experiment (IAN022) ending in June 1999. We estimate that a further nine studies have taken place since that time; the reports relating to them not being part of the acquired cache of documents.

Following the *It's a Dog's Life* scandal, the most common errors have involved the recording of operation times including ischaemia times (71 failures), food consumption (39), fluid intake and urine output (27) and haematology (26). Additionally, a full 39 out of 143 transplanted "donor" kidneys were not weighed at the time of surgery.

The 39 study reports that have been acquired are in final *draft* form. Only in respect to four organ transplant studies have the final, fully edited versions been obtained – and in three of these four, errors are recorded that were not acknowledged in the earlier drafts. For example, the study reports for IAN007 and IAN013 list no departures from Good Laboratory Practice, whereas the final reports record four departures, at least one of which appear to be significant²³⁴:

"The failure to undertake chemical analysis of formulated materials to demonstrate achieved concentrations and determination of homogeneity and stability."

In addition, the final report for IAN013 contains File Notes not included in the draft report. These notes acknowledge that record-keeping relating to the collection and disposal of immunosuppressant doses was inadequate. They also admit that there was incomplete documentation covering the general performance of the study. Both of these acknowledged lapses constitute a breach of Standard Operating Procedures (SOPs) and/or of GLP.

The draft report for study ITN18 lists no exceptions to GLP compliance, but the final report issued by HLS includes five exceptions. In addition to the four that appeared in the final reports for the studies highlighted above, another interesting departure is noted:

"[redacted] [trade name for [redacted]], Batch 109 1094 used for the study, had no expiry date stated nor was the Sponsor able to provide one. An expiry date of 3 years from the date of manufacture was, however, noted from other batches. The expiry date of this batch was therefore assumed to be 10.1997 which covered the period of use of this material for this study."

²³⁴ Curiously, these same two final reports reveal that - with one exception - the laboratories the Sponsor (i.e. Imutran) used to undertake blood and tissue investigations are not part of the UK GLPMA compliance programme. As a result, compliance is not claimed for these analyses.

The fourth final report obtained is for IAN002. Departures from GLP compliance detailed in this final text are also recorded in the earlier draft version.

7.7 Imutran continue to look for alternatives to HLS

Imutran had considered alternative venues in which its xenotransplantation research could be carried out in 1996. Come September 1998 and the search was continuing, or had perhaps been revived. A draft document (“[REDACTED] Assessment”) examines the possibility of moving the primate research programme to [REDACTED], a laboratory at [REDACTED]. The document states:

“The primary objectives of the assessment was to evaluate the facilities, staff expertise, building qualifications and likely cost of transplants performed at [REDACTED], particularly in the light of the recent proposals from Huntingdon Life Sciences.”

Precisely what HLS’s “recent proposals” were is not made clear. However, during Autumn 1998, Imutran and HLS had been negotiating a new study contract. Imutran decided to remain with HLS, although the new contract, which commenced 2 November 1998, did give Imutran the option of terminating the agreement with six months notice.²³⁵ A letter from [REDACTED] (Imutran) to [REDACTED] ([REDACTED], HLS) dated 9 December 1998²³⁶, suggests that Imutran had been struggling to secure an increased resource commitment from HLS, and worries were already arising over whether HLS would fulfil the conditions of the new agreement:

“... I am a bit concerned as it has just be [sic] brought to my attention that, due to logistic problem at HLS, we may not be able to perform more than 5 transplants in January 1999. Does this correspond to reality? This would clearly raise some concerns as it would conflict with one of the major improvements we expect from the new study agreement. Could you please give us assurance that you will be in a position to fulfil the conditions as outlined in the new contract.”

7.8 “Further Drug Administration Error” and procedural failures at HLS

Less than a month later, Imutran’s frustration with HLS is given vent in a letter from [REDACTED] to [REDACTED], [REDACTED] at HLS. Dated 6 January 1999 and entitled “Further Drug Administration Error”²³⁷, [REDACTED] begins his letter with an unequivocal remonstration:

²³⁵ See files at [REDACTED] and [REDACTED]

²³⁶ See file [REDACTED]

²³⁷ See file HLSAPP7C.1.

“Unfortunately, I cannot refrain from expressing to you – on behalf of Imutran Ltd – our serious concerns in the light of the latest events recently occurring at HLS.”

█████’s dismay centred on two incidents that had occurred in the previous month during the course of a study entitled “HETEROTOPIC RENAL XENOGRFT TRANSPLANTATION IN CYNOMOLGUS MONKEYS WITHOUT SPLENECTOMY”.²³⁸

“On 22 December 1998 due to a misfiling of dose sheets, **animal A178 was exposed to a dose of █████ which was four fold higher than recommended.**”

Then, “as if this were not serious enough,” as █████ puts it, “the blood sample for the █████ trough level of Animal A464 was taken 2 hours after the administration of the compound – instead of immediately prior to its administration.” [see below for the significance of this error]

“**Clearly this situation is unacceptable,**” laments █████.

Although █████’s comments are damning enough in themselves, the calamitous nature of the first incident becomes apparent when studying the final draft report on the experiment. The episode involved a female cynomolgus monkey who had been transplanted with a transgenic pig kidney 29 days earlier on 23 November 1998. On the morning of 22 December - the day of the “drug administration error” - instead of the usual █████ she was given █████. She died the following day.

According to HLS’s own observations, this was her harrowing experience during the last two days of her life²³⁹:

29	am	Quite subdued, liquid faeces, puffy around eyes.
	pm	Alert but quiet and huddled, puffy around eyes, appears inactive.
30	am	Huddled on perch, head raised only when stimulated, face swollen especially around eyes, eyelids nearly closed, unsteady on perch, does not move when stimulated.
	pm	Noted prior to sedation: Very quiet, unsteady, body tremors, grinding teeth. Sedated and euthanased.

The second incident about which █████ had become exercised also occurred during the course of study IAN020. This was a failure to monitor properly the male monkey’s blood for levels of █████ – an immunosuppressant drug that is administered both prior to and after transplant surgery. Measurements of █████ blood levels were the means by which Imutran set the “optimum” dose of the drug in an attempt simultaneously to minimise side-effects and overcome the rejection process.

²³⁸ See study report IAN020.

²³⁹ See clinical signs for study IAN020.

The final draft report for this study describes the dosing procedure for [REDACTED] as follows:

“[REDACTED] was initially administered as [REDACTED] by oral administration on Days [REDACTED] and [REDACTED] at a dosage of [REDACTED] twice a day, morning and afternoon/evening. A dosage of [REDACTED] was also administered in the morning on Day [REDACTED]; thereafter administration of [REDACTED] continued at a dosage level advised by the Sponsor and was given by gavage as split dose morning and afternoon/evening.” (my emphasis) “After a few days the immunosuppressive regime was then individually tailored for each animal being based on the results of laboratory investigations and blood drug levels.”²⁴⁰

The failure to take the blood sample at the specified time would, therefore, have made it difficult to judge how much [REDACTED] should be given either to manage graft rejection or to deal with other clinical problems.

In fact the error amounted to an elementary failing, given that the principal objective of the study was to produce information regarding the effectiveness and tolerance of immunosuppressive treatments in pig-to-primate xenotransplantation

The animal concerned (A464) survived just four more days, though his demise appears to have been due to another blunder. The team of vivisectioners left a foreign body – a swab – inside him following the transplant procedure. This opened the way to a bacterial attack, leading to rapid and fatal sepsis of the spleen.²⁴¹

[REDACTED]’s letter to HLS (6 January 1999) informs us that Imutran had contracted for sufficient resources for eight transplanted animals. At the time of the first incident, there were five living animals; and by the time of the second, just two. The blunders should not, therefore, have been caused by a resource shortfall. [REDACTED] is led to a scathing conclusion:

“Frankly, I do not understand how this could occur as every step in the procedures is double checked by a second person. I can only believe that the double check procedure is not in place or that it is not taken seriously by the people looking after Imutran’s animals.”

The affair suggests strongly that the malaise Parliament and the public had been led to believe had been overcome following the *It’s a dog’s life* controversy remained entrenched at HLS more than a year later.

In his reply of 15 January 1999,²⁴² [REDACTED], HLS’s [REDACTED], is appropriately abject and unequivocal in his apology. [REDACTED] confesses to Imutran:

“We would like to take this opportunity to apologise for the recent errors that have taken place at Huntingdon during the ongoing Xenotransplantation work. There are no excuses that can be made for the failure of individuals to follow

²⁴⁰ See study IAN020, p.15.

²⁴¹ See files at HLSAPP7A and HLSAPP7B

²⁴² See files at HLSAPP7D

the operating procedures that have been set down to ensure the smooth conduct of studies...

We would like to end by re-iterating apologies both from a personal viewpoint and from the viewpoint of the Company, and hope that the changes recently instituted will provide the necessary trained resource to meet your expectations.”

The improvements ██████████ referred to consisted of “significant changes in the management structure and operating reporting lines”.

However, such changes were supposed to have been instituted by HLS 16 months earlier as part of the 16 Home Office conditions for retaining the establishment’s Certificate of Designation.

Condition (iii) had required:

“That summary findings of the Department of Health Good Laboratory Practice scrutiny be disclosed by the establishment to the Home Office with confirmation that any process problems have been corrected.”

In turn, some of the *minimum* responsibilities of test facility management laid down by the GLP regulations²⁴³ include:

“[E]nsure that a *sufficient number of qualified personnel*, appropriate facilities, equipment, and materials are available for the timely and *proper conduct* of regulatory studies;” (my emphasis)

“[E]nsure that personnel clearly understand the functions they are to perform and, where, necessary, provide training for those functions;”

“[E]nsure that appropriate and technically valid standard operating procedures are established and *followed*, and approve all original and revised standard operating procedures;” (my emphasis)

Condition (vi (b)) had further stipulated:

“That the applicant be required to satisfy the Home Office that line management arrangements for all animal care staff are effective. Specifically... that only trained and competent staff are entrusted with responsibility for the care and welfare of animals.”

Once more, HLS’s own words call into question the notion that they had fulfilled the 16 conditions. Equally, it must be concluded that either the Home Office made insufficient effort to monitor HLS at this critical time; or that it was aware of the failings but was not serious in its professed intention to hold HLS to account.

²⁴³ Schedule 1, Part I, 1 (2 (b), (d) & (e)).

7.9 Imutran/Novartis finally terminate work at HLS?

Towards the end of 1999, another serious weakness in Imutran's primate xenotransplantation research programme began to emerge. An Imutran internal email from [REDACTED]

[REDACTED] dated 17 September 1999²⁴⁴ contains this passage:

"I have read your meeting minutes from the 'Task Force' meeting of 27th August and over the past couple of weeks put a lot of thought into how Imutran management (and you and I in particular!) addresses the **severe problems** posed by the current state of the primate research data." (my emphasis)

While these 'severe problems' are not spelt out, some five months later the whole HLS programme is frozen following discussions between [REDACTED] for Novartis (Imutran's parent company) and [REDACTED], Imutran's [REDACTED]. An email circulated by [REDACTED] on 3 February 2000 stated the following:

"In view of the recent experimental failures and as discussed with [REDACTED], I would like you to interrupt any further experiments until better understanding of the reason for these failures has been determined."²⁴⁵

Later the same day, [REDACTED] sent an email to [REDACTED], in which she confirmed their decision to halt the HLS programme, and specified other reasons for having done so:

"I have interrupted the programme at HLS until there is:

- a process for retrospective reporting of past studies in place based on checked, secured raw data
- the management control measures in place for future primate studies to allow the programme to be performed [in an (? - bad photocopy)] appropriately controlled fashion.

Ten days later, another internal Imutran document points a finger directly at HLS. Entitled "Primate Transplantation: Data and Process Review,"²⁴⁶ it contains the following:

"Data from various sources (principally HLS) are present in incomplete paper form..."

Imutran were by now penalising HLS for the late production of final reports at a cost of £1000 per month per report. A letter from Imutran's [REDACTED] and [REDACTED] to [REDACTED] at HLS (15 March 2000) confirms the deduction of £5,000 from a HLS invoice for the non-delivery of five final reports.²⁴⁷

²⁴⁴ See file HLSAPP8B.1

²⁴⁵ See files at [REDACTED]

²⁴⁶ See files at [REDACTED]

²⁴⁷ See file [REDACTED]

Two further documents - that seem to have been compiled around the beginning of 2000 - suggest that Imutran have, or are about to, terminate the entire primate xenotransplantation programme at HLS. In one of the documents, a table has been compiled listing various Novartis xenotransplantation research budget holders (see below).²⁴⁸ The objective of the exercise seems to be to identify possible cost savings for year 2000. The table suggests that Imutran/Novartis had originally expected to spend £1.3 million at HLS during 2000. But there now appeared to be no current contract with HLS; though there was reference to “Legal assessment of possible penalties ongoing” - penalties that would fall to Imutran itself. What these penalties were and the reason for them are not set out. But a sentence in the document’s Comment section suggests that, at issue was the compensation Imutran would have to pay HLS were they to end their contract:

“Terminate. 20% contingency for termination costs.”

7.10 The Future of Imutran’s Xenotransplantation Research Programme

Irrespective of the frustrations Imutran have expressed throughout this report about the way HLS have conducted their research, the commissioning company were themselves facing severe difficulties. These related to the extremely poor survival times of monkeys who had been subject to xenotransplantation procedures using organs taken from Imutran’s vaunted hDAF transgenic pig.

A confidential document (9 April 2000) produced by [REDACTED], [REDACTED], [REDACTED] and [REDACTED] at Imutran outlines a radical new programme whose purpose is to “achieve substantial improvements in survival rates”. The document is called “Primate Development Plan” and its centrepiece is a collaborative experimental programme using a network of seven research centres throughout Europe and North America. Transgenic pig breeding centres had been established on both continents in order to supply the collaborators with organs for xenografting.

HLS is not listed as part of this external collaborative network²⁴⁹ and the April 9 report goes on to state:

“Since 1Q of 2000 the in-house pig-to-primate transplant program has been discontinued, so that all efforts to improve transplantation data now fully rely on external collaborations.”²⁵⁰

Based on other documents, however, it is still not clear whether HLS was at this time contracted to conduct any xenotransplantation experiments on behalf of Imutran. One document, for instance - apparently written at the end of 1999 or beginning of 2000 - seems to be a draft of a submission to the Home Office²⁵¹ asking for amendments to

²⁴⁸ See file [REDACTED]

²⁴⁹ See file [REDACTED]

²⁵⁰ See file [REDACTED]

²⁵¹ See files at [REDACTED]

an existing project licence which would lead Imutran's research at HLS to focus on testing novel strains of transgenic pigs; these novel strains would express human regulators of complement activity different from hDAF. Whether such a proposal was ever submitted, or whether it was submitted and refused is presently unknown.

7.11 HLS and xenotransplantation research: a summary

The programme of xenotransplantation research designed and commissioned by Imutran is ethically and legally controversial because of the intensive suffering inflicted on higher primates and pigs, the low probability of any human benefit arising, and the potential danger posed to human health.

The conduct of experiments at HLS adds extra spice to this contentious research because of HLS' own chequered history. In particular, the *Countryside Undercover* documentary, 'It's a Dog's Life', screened in March 1997 provoked fierce criticism of HLS from a normally sympathetic Home Office and Animal Procedures Committee (APC) because of revelations of "brutality" on the part of the company's employees, and breaches of the establishment's Certificate of Designation which licences it to carry out animal experiments. Indeed the Home Office threatened to revoke HLS' Certificate because of the findings of *Countryside Undercover*.

The criticism did not stop there. The documentary also uncovered breaches of the principles of Good Laboratory Practice (GLP) which are designed to ensure the proper conduct of studies so that the data generated is trustworthy. The Government's GLP Monitoring Authority (GLPMA, part of the Department of Health) issued HLS with a Warning Notice after it "found a number of serious deficiencies in their GLP procedures." As a result of this Warning Notice, HLS were in danger of being prevented from conducting regulatory tests, potentially an even greater blow than losing their licence to vivisect.

HLS managed to survive because in autumn 1997 the Home Office and the GLPMA deemed that the company had put their house in order. These judgements, greeted with scepticism by animal protection groups at the time, have never been open to public scrutiny until the publication of this report and the internal documents upon which it is based. We believe that the full story casts grave doubts on the validity of the Government's absolution of HLS.

Early GLP deficiencies

The internal documents now disclosed suggest that the GLP problems identified in the dog toxicology unit at HLS by *Countryside Undercover* and confirmed by the GLPMA were not unique. As early as February 1996, Imutran reports were identifying a "fundamental shortfall in GLP compliance" in studies conducted at HLS.

The main text links several specific GLP regulations to the problems identified by Imutran. One Imutran inspector, [REDACTED], claimed that three studies already

completed had exhibited “a fundamental shortfall in GLP compliance, and: “There is a chasm that needs to be bridged rapidly if future Imutran studies are to be compliant with GLP.” Imutran were evidently less than confident in HLS’ ability to provide a service that matched up to their expectations: two months later they considered dumping HLS for an alternative venue for their research programme, an exercise repeated in September 1998.

Because of the time that has elapsed since these studies, any action on the part of the GLPMA with respect to potential GLP failures may appear superfluous. But it is worth considering the following chain of events. Let us assume that Imutran were correct in their attributions of fundamental shortfalls in GLP compliance at HLS in early 1996 (and we have no reason to think they would be unjustifiably critical of HLS). This was followed by the “serious deficiencies” found by the GLPMA at HLS following *Countryside Undercover* related to studies in the autumn of 1996. If the GLPMA had been aware of Imutran’s findings and concurred with their conclusions, they may well have judged that the deficiencies in GLP for the xenotransplantation studies at HLS would have warranted a Warning Notice. The *subsequent* failures confirmed in the dog toxicology unit that arose from the Countryside Undercover investigation may thus have led to HLS’ ejection from the GLP compliance programme. This would probably have resulted in the closure of HLS.

Despite the forthright claims of GLP failure made by Imutran, the studies for which GLP compliance was considered fundamentally deficient are presented as generally compliant with GLP by HLS in the final *draft* study reports issued over two years later. We believe that there are sufficient grounds for this issue to form part of the remit of an independent judicial enquiry into the xenotransplantation research programme.

One of the overarching reasons proposed by Imutran for HLS’ shortfalls in GLP compliance was a clash of cultures between the demands of Imutran’s research and HLS traditions and practices. Taken together with the specific problems outlined above, then the regulatory implications go beyond the remit of the GLPMA. In fact, they bring into question the validity of the Home Office’s decision to licence this project at HLS: one of the factors to be taken into account by the Home Office in its deliberations is “whether the facilities at the establishment are adequate for the scientific procedures.”

Most importantly, given the severe suffering inflicted on 120 higher primates 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.

Did HLS really satisfy the 16 conditions?

Following the Countryside Undercover documentary in March 1997, the Home Office imposed 16 conditions which HLS were charged with fulfilling in order to retain their Certificate of Designation to conduct animal experiments. In September, the Home Office re-issued the Certificate to HLS claiming in Parliament that the company had satisfied all the conditions.

For the first time, this report can provide the public and Parliament with an inside view of whether HLS really did satisfy the 16 conditions. We believe that the truth revealed here is a severe embarrassment for both HLS and the Home Office because it throws into serious doubt the validity of the Home Office's decision to re-issue HLS' Certificate.

One devastating disclosure presented here is the revelation that less than six weeks after HLS had regained its Certificate, a serious breach of the law took place at the establishment – the illegal re-use of animals in experiments without Home Office permission – which should have been prevented by compliance with the 16 conditions.

According to an Imutran record of the affair, the illegal act resulted from a breakdown in communication at HLS. Two HLS staff are said to have “confirm[ed] that the error lay within HLS and no Imutran staff are at fault.” Imutran responded: “It is clear from what you said that any remedial actions that may be required lay within HLS, and were not the result of an error here at Imutran,” although subsequently HLS managers vehemently protested their innocence.

The fifth condition set by the Home Office had stated:

“That adequate provision has been made for regular and effective means of communication between those entrusted with responsibilities under the Act.”

Furthermore, an analysis of the final draft study reports on five studies which took place during and shortly after the period when HLS were supposedly fulfilling the 16 conditions intensifies scepticism about the Home Office's reinstatement of HLS' Certificate. The reports reveal a catalogue of errors and omissions that potentially undermined compliance with GLP. The third Home Office condition had demanded:

“That summary findings of the Department of Health Good Laboratory Practice scrutiny be disclosed by the establishment to the Home Office with confirmation that any process problems have been corrected.”

In fact, throughout the course of this research programme we estimate that 520 separate data recording errors and failures took place before during and after HLS' ‘fulfilment’ of the 16 conditions.

“Further Drug Administration Error”

Perhaps the most startling calamities at HLS are revealed by correspondence dated January 1999. The letters themselves tell a powerful story as Imutran's [REDACTED] berates HLS for an accidental quadruple overdose of one monkey who died the following day, and the failure to take an important blood sample at the arranged time:

“Unfortunately, I cannot refrain from expressing to you – on behalf of Imutran Ltd – our serious concerns in the light of the latest events recently occurring at HLS...

Clearly this situation is unacceptable... Frankly I do not understand how this could occur as every single step in the procedures is double checked by a second person. I can only believe that the double check procedure is not in place or that it is not taken seriously by the people looking after Imutran's animals."

██████████ apologises profusely on behalf of HLS:

"We would like to take this opportunity to apologise for the recent errors that have taken place at Huntingdon during the ongoing Xenotransplantation work.

There can be no excuses that can be made for the failure of individuals to follow the operating procedures that have been set down to ensure the smooth conduct of studies.

We would like to end by re-iterating apologies both from a personal viewpoint and from the viewpoint of the company, and hope that the changes recently instituted will provide the necessary trained resource to meet your expectations."

In addition to the potentially devastating impact these failures may have had on animal welfare, they also represent evidence of manifold GLP shortfalls as well as undermining further the notion that HLS really did satisfy the 16 conditions set by the Home Secretary.

The current situation

Imutran appear to have "severe problems" with the state of the data from their primate research programme, a situation for which HLS would seem to hold at least some responsibility. The latest documents suggest that Imutran have terminated their research at HLS and moved their primate vivisection programme to seven collaborative centres in Europe and North America.

Index of filed documents accompanying PART IV: HUNTINGDON LIFE SCIENCES

HLSAPP1.1→1.5: “Subcontractor Inspection Report” by [REDACTED], Imutran, 8 February 1996.

HLSAPP2.1→2.6: “A report on the Good Laboratory Practice (GLP) status of historical studies conducted at Huntingdon Life Science on behalf of Imutran and recommendations for improvement” by [REDACTED], Imutran, 28 February 1996.

HLSAPP3.1→3.6: [REDACTED]
[REDACTED]

HLSAPP4A.1: “LATE ARRIVAL OF BLOOD SAMPLES,” fax to [REDACTED]
[REDACTED] (HLS) from [REDACTED] (Imutran), 23 October 1996.

HLSAPP4B.1: Fax to [REDACTED] (HLS) from [REDACTED] (Imutran), 13/12/96.

HLSAPP5A.1→5A.6: “A report on the Accidental re-use of animals under Project Licence PPL 80/848,” (including accompanying correspondence) [REDACTED], 13 January 1998.

HLSAPP5B.1 & 5B.2: Internal Imutran Memorandum from [REDACTED] to [REDACTED] (then [REDACTED]), 9 August 1995.

HLSAPP6A.1 & 6A.2: [REDACTED]
[REDACTED]

HLSAPP6B.1: [REDACTED]
[REDACTED]

HLSAPP6C.1→6C.5: [REDACTED]
[REDACTED]

HLSAPP6D.1: [REDACTED]
[REDACTED]

HLSAPP7A.1→7A.3: Clin/Path Meeting Minutes, Imutran/Novartis, 22nd January 1999

HLSAPP7B.1 & 7B.2: “Database entries,” letter from [REDACTED] (Imutran) to [REDACTED]
[REDACTED], 14 May 1999.

HLSAPP7C.1: “Further Drug Administration Error,” letter from [REDACTED] (Imutran) to [REDACTED]
[REDACTED] ([REDACTED], HLS), 6 January 1999.

HLSAPP7D.1 & 7D.2: Fax from [REDACTED] to [REDACTED], 15 January 1999.

HLSAPP8A.1: [REDACTED].

HLSAPP8B.1: “Primate review report”, internal Imutran email from [REDACTED] to [REDACTED], 17/09/99

HLSAPP8C.1→8C.5: [REDACTED]
[REDACTED].

HLSAPP8D.1: [REDACTED]
[REDACTED]

HLSAPP8E.1 & 8E.2: [REDACTED]
[REDACTED]

HLSAPP9A.1→9A.19: [REDACTED]
[REDACTED]
[REDACTED]

HLSAPP9B.1→9B.11: [REDACTED]
[REDACTED]

PART V

THE WAY FORWARD

CHAPTER 8

Conclusions and Recommendations

8.1 Relating the evidence to the ethical and regulatory framework

Higher primates and pigs

The primary focus of this report and the documents upon which it is based has been the use of species of higher primates – the ‘cousins’ of human beings’ – in intensely painful and traumatic research. Such use of non-human primates is particularly controversial because their relatedness to humans renders their substantial intelligence, complexity and sensitivity hard to deny. Our society is beginning to recognise the moral duties owed to higher primates by virtue of their qualities and capacities. This realisation has manifested itself in the ban on the use of Great Apes in the UK announced in late 1997, and the current consideration by the Government advisory committee on animal experiments, the Animal Procedures Committee (APC), of a prohibition on research on any primate species. In the context of these deep movements in ethical attitudes and the slow percolation of these more enlightened attitudes into law, the justifiability of Imutran’s primate xenotransplantation programme appears increasingly contentious.

We anticipate that by publishing the documents relating to this research programme and producing this report, a unique and historic contribution will be made to this momentous debate because of the volume and quality of the information we have made available. Now, the public has the clearest view of a practice traditionally shrouded in secrecy, thus enabling them to make a more informed decision about these matters. We are pleased to be able to make this important contribution to the democratic process.

We believe that reflection on the evidence provided by the documents and this report about the crushing impact of research on primates will lend a sense of urgency to the APC’s current deliberations concerning a ban on experimentation on primates. It is hoped that such a ban is implemented swiftly in recognition of the ethical duty of respect that we owe to such animals.

Thousands of pigs have also been exploited and killed in the course of this research programme. It is widely acknowledged that pigs are particularly complex, intelligent and sensitive animals, at least on a par with dogs. We hope that the aforementioned debate sparked about the moral status of nonhuman primates matures into an objective and compassionate examination of our society’s treatment of all animals.

Absolute legal limits on suffering

Fundamental legal limits to the suffering that can be inflicted on animals in laboratories are enshrined in UK and European legislation. Paragraph 5.42 of the Guidance on the Operation of the Animals (Scientific Procedures) Act 1986 states: "The Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated." Furthermore, Article 8 of the European Directive 86/609 stipulates: "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.**" (added emphasis).

We contend that these basic safeguards have been breached in the course of this xenotransplantation research programme. Here are a few examples:

Baboon W205m was used in study ITN6, which saw transgenic piglet hearts implanted into the necks of the primates. This is the record of his last 12 twelve days of life:

9	am	Quiet but alert. Vomit in cage.
	pm	Quiet but alert.
10	am	Quiet but alert.
	pm	Quiet but alert.
11	am	Quiet but alert. Occasionally huddled.
	pm	Quiet and huddled. Transplanted heart seems very large and possibly discomforting animal. Neck swollen.
12	am	Quiet and huddled. Holding neck. Appears unsteady.
	pm	Quiet and huddled. Holding neck. Appears unsteady.
13	am	Quiet and huddled. Holding neck. Appears unsteady.
	pm	Quiet and huddled. Supporting neck with left arm. Unsteady when moving.
14	am	Quiet and huddled. Transplanted heart swollen and red, seeping yellow fluid.
	pm	Quiet and huddled. Transplanted heart swollen and red, seeping yellow fluid.
15	am	Quiet and huddled. Transplanted heart appears swollen. Yellow fluid around swelling.
	pm	Quiet and huddled. Transplanted heart appears swollen. Yellow fluid around swelling.
16	am	Quiet and huddled. Transplanted heart appears swollen. Animal picking at transplant site. Yellow fluid around swelling.
	pm	Quiet and huddled. Transplanted heart appears swollen. Animal picking at transplant site. Yellow fluid around swelling.
17	am	Quiet and huddled. Swollen around site of transplanted heart. Yellow fluid around wound, feels warm to the touch.
	pm	Quiet and huddled. Swollen around site of transplanted heart. Yellow fluid around wound, feels warm to the touch. Approximately 12 ml of purulent fluid aspirated.
18	am	Quiet and huddled. Swollen around site of transplanted heart. Yellow fluid seeping from site, also some dry scabs.
	pm	Quiet and huddled. Swollen around site of transplanted heart. Yellow fluid seeping from site, also some dry scabs.
19	am	Quiet and huddled. Scar on neck appears dry.
	pm	Quiet and alert.
20	am	Quiet but alert. Scab on operation site appears clean and dry. Keeps holding area where transplanted heart is.
	pm	Quiet and huddled. Little movement and unsteady when moving. Showing signs of discomfort.
21	am	Quiet and huddled. Scab on operation site appears dry. Reluctant to move. Marked firm swelling around implant. Animal showing obvious discomfort. Fluid swelling developing in sub-mandibular region.
	pm	Sero-sanguinous fluid drained but no purulent material. Transplanted heart beat barely palpable. Swelling so large animal sacrificed for humane reasons.

X225m died in study ITN19, which transplanted pig hearts into the abdomens of baboons and left their own hearts in place:

9	am	Quiet but alert. Normal faeces. Swollen right arm around injection site, possible local infection. Rectal temperature 39.3°C.
	pm	Quiet, sitting at front of cage, reluctant to move, reluctant to use right arm. Loose faeces.
10	am	Quiet, huddled at front of cage, becomes alert when stimulated. Slightly unsteady, reluctant to move. Little/no use of right arm. Normal faeces.
10	pm	Quiet but alert, occasionally huddled. No use of right arm which appears swollen.
11	am	Quiet but alert. Right arm badly swollen and bruised.
	pm	Quiet but alert. Right arm badly swollen and bruised.
12	am	Quiet but alert. Right arm still swollen, skin broken and oozing blood.
	pm	Quiet but alert on perch. No faeces seen. Transplanted heart beating.
13	am	Quiet and slightly huddled. Right arm swollen.
	pm	Quiet and huddled. Right arm swollen with large open wound, heavily bruised, not bleeding. Vomit during dosing. Transplanted heart beating.
14	am	Quiet but alert, sitting at front of cage. Slow movement. Large open wound on right arm, discharging pus. Normal faeces.
	pm	Quiet but alert, moves when stimulated. Wound on right arm larger than observed earlier.
15	am	Quiet and huddled, sitting on perch. Reluctant to use right arm. Further wound breakdown. Scarified for humane reasons.

X240f was also used in study ITN19, she clung to life for 99 days, the longest survival time in the entire research programme. This is what she went through in her last eleven days:

88	am	Alert, sitting on perch. Normal faeces.
	pm	Sitting on cage floor, active when stimulated.
89	am	Quiet and huddled, seems tired. Rectal temperature 40.6°C.
	pm	Quiet and huddled, seems tired, reluctant to move from perch.
90	am	Quiet and huddled, seems tired. Rectal temperature - within normal range.
	pm	Quiet and huddled, seems tired. Rectal temperature - within normal range.
91	am	Quiet but alert, occasionally active.
	pm	Quiet but alert, occasionally active.
92	am	Quiet and huddled, reluctant to move. Exhibits discomfort when moving, especially right leg.
	pm	Quiet and huddled but alert, some movement seen.
93	am	Quiet but alert, sitting on perch, seems to have difficulty walking.
	pm	Quiet but alert, sitting on perch.
94	am	Quiet and huddled. Loose faeces.
	pm	Quiet but alert, not very active. Transplanted heart beating satisfactorily.

95	am	Quiet and huddled on perch, reluctant to move. Body and head tremors. Normal faeces.
	pm	More alert and active than noted in the morning.
96	am	Quiet and huddled on perch but alert, little movement. Some limb tremors.
	pm	Quiet and huddled on perch but alert, little movement. No faeces seen. Large vomit in cage.
97	am	Quiet and huddled on perch. Vomit in tray. Normal faeces.
	pm	Quiet but alert, sitting on perch. transplanted heart beating satisfactorily.
98	am	Quiet but alert, sitting on ladder. Reluctant to move. Normal faeces.
	pm	Quiet but alert, sitting on ladder. Seems unsteady at times.
99	am	Quiet but alert. Normal faeces. Scarified for humane reasons.

Furthermore, these were not isolated cases, as the report and documents testify. **The European Directive forbidding the infliction of severe suffering may also be relevant to Imutran's research collaborations in Spain and Italy.**

The levels of suffering endured by the primates used in Imutran's xenotransplantation research has been such that the adherence of the procedures to the fundamental legislative requirements designed to prevent severe suffering is surely in doubt.

In fact, scrutiny of the xenotransplantation protocols and their likely effects leads us to conclude that there was an inherently high risk of severe suffering occurring: indeed it would be inevitable. The surgery itself has been highly invasive, especially so in the case of orthotopic heart transplants where the primate organ was directly swapped for a piglet's organ and required the splitting of the breastbone. The implantation of piglet hearts into the necks of baboons also invites severe suffering. However, perhaps the most acute suffering occurred as a result of the inevitable complications arising from the rejection of the organ leading to organ failure, and the toxicity and infection risks associated with the immunosuppressive drug regimen.

For example, the effects of renal failure and associated blood poisoning are undoubtedly severe: nausea, vomiting, lethargy, drowsiness and death. Drug toxicity also led to nausea and diarrhoea. Infections threatened animals with inflammation of the lungs and accompanying breathing difficulties.

We do not think that these effects were difficult to predict. Therefore, there are question marks over whether such research should ever have been licensed by the Home Office in the first place because of its intrinsic risk of severe suffering – in breach of UK and European law.

The gravity of this issue and the weight of supporting evidence for severe suffering warrant the institution of an independent judicial enquiry to examine not only who may have been directly at fault for permitting such distress (e.g. the project licence holder or the Named Veterinary Office, who both have relevant legal responsibilities under the Animals (Scientific Procedures) Act 1986), but also the conduct of the Home Office in licensing such research in the first place and failing to prevent such suffering during the subsequent five years of

vivisection. It is this charge of culpability directed at the Home Office which is one of the necessitating factors for an independent enquiry.

Other regulatory issues

Several other incidents have been brought to light through the publication of the acquired documents:

- The deaths of three primates en route from the Philippines to the xenotransplantation research laboratories at Huntingdon Life Sciences (HLS). The inadequate space and ventilation in the transport crates were thought to be contributory factors. Apart from the important ethical issue of the suffering of the animals in the course of this journey, which lasted 48 hours, the crates also breached fundamental requirements of international air transport regulations. The Home Office did not disclose these breaches in a Parliamentary answer on the question, nor did they answer the question which enquired whether the animals were destined for xenotransplantation research.
- One confirmed incident where the journey times were significantly longer than the time estimated on Imutran's application form: 34 hours instead of 20-24 hours. The application was approved "in accordance with the details supplied." The ill-fated 48 journey from the Philippines to the UK may also have failed to correspond with the stated estimated time for that journey, which was typically 30 hours for identical shipments.
- The illegal re-use of animals at HLS – one month after the Home Office had re-issued the company with a Certificate of Designation to conduct animals tests on the basis that it had successfully implemented a raft of improvements designed to ensure adherence to regulations. Yet HLS were allowed to retain their Certificate.
- The incarceration of wild-caught baboons throughout the second half of 1999 and into 2000, despite an apparent commitment made by Imutran to use the baboons as quickly as possible in recognition of the suffering they would experience – according to a HLS manager - as a result of being "in what must seem to them to be small enclosures."²⁵²
- The question of the eventual fate of these baboons who had been imported for the stated purpose of xenotransplantation.
- The relationship between the Home Office and Imutran as evidenced by comments such as this one made by Imutran's CEO in 1995 about a forthcoming meeting with a Home Office Inspector: "We have to work to make him look like a jolly good bureaucrat and yet achieve our goals as well!"²⁵³

²⁵² See file WCB26.1.

²⁵³ See File I3.1.

This is another revealing statement that describes the communication between Imutr and another Home Office Inspector, [REDACTED]: “[REDACTED] has on several occasions expressed his view that the new License will be approved before the existing license is revoked and that Thursday [i.e. a meeting of the APC to discuss the licence application] will be merely a ‘rubber stamping’ exercise.”²⁵⁴

Once again, concerns are not limited to the need to identify those responsible for any breaches and to apply any necessary legal sanctions; the adequacy of the Home Office’s response is also debatable. Hence, further weight is lent to the call for an independent judicial enquiry.

The cost/benefit assessment

In addition to ensuring adherence to prescribed limits to the suffering endured by animals, as well as other requirements described in the previous section, the Home Office is duty-bound to weigh the costs to the animals in the course of research against the benefits likely to accrue from the programme of animal experimentation in question. These are the features of the crucial cost-benefit assessment described by the head of the Home Office Inspectorate charged with scrutinising applications to conduct vivisection:²⁵⁵

- *“Judgement on the likely severity of the adverse effects on animals”*

We have argued at length that the evidence demonstrates that the effects were severe, and predictably so.

- *“Standards of care and accommodation”*

The welfare impact on wild-caught baboons of incarceration in a laboratory has already been referred to. Other bioethical reports (e.g. the Nuffield Report on the ethics of xenotransplantation) have identified the negative impact on animal welfare of keeping primates in laboratory conditions. One must also take into account the conditions endured by the animals in transit to the UK for the purpose of this research.

The lengthy and intense suffering endured by the primates in the course of the experiments raises concern about the adequacy of the care given to the primates, particularly in terms of prompt euthanasia.

Furthermore, the requirements to keep pigs in qualified pathogen free environments and the utilisation of surgical derivation and early weaning techniques have been acknowledged by the Home Office to have a negative impact on these animals.

²⁵⁴ See File CY24.2.

²⁵⁵ Report of the Animal Procedures Committee for 1997, p.50-59.

- *“Technical competence of the people and establishments to be involved in the project”*

Following two inspections, Imutran themselves concluded that there was a “fundamental shortfall in Good Laboratory Practice compliance” for some of their studies at HLS. Imutran then went on to state that they would have “to accept that the service from HLS will fall short of their expectations.” We have identified 520 experimental readings that were not recorded in error during the course of this research project.

There is also serious concern about the apparent transplantation of seven baboons who seem to have been positive for the lethal (to humans) Simian Herpes B Virus. This is particularly significant because of the employment of transplant surgeons [REDACTED] to conduct these vivisection procedures who may then have gone on to operate on immunosuppressed patients – an issue emphasised by a Government expert on infectious diseases. Furthermore, the baboons appear not to have been tested for a crucial antibody before surgery.

Other failures include: the illegal re-use of animals at HLS; the quadruple overdose of a monkey who died the following day and the failure to take an important blood sample a month later – incidents that provoked severe criticism from Imutran and profuse apologies from HLS; the leaving of a swab inside a monkey after surgery that caused his spleen to go septic, resulting in his death; the accidental freezing of a kidney during transplantation resulting in the sacrifice of the intended primate recipient; conflicting pathology data leading Imutran management to express the fear that the company’s ISO9000 status may have been jeopardised; the acknowledgement in early 2000 of “severe problems” with the state of the data for these studies.

Apart from the relevance of these events to the cost-benefit assessment, they also raise doubts about the compliance of the primate vivisection programme to Good Laboratory Practice (GLP). We have, therefore, passed this report to the GLP Monitoring Authority at the Department of Health with a view to initiating an enquiry into the level of adherence to GLP Regulations.

- *“Relevance of the animal ‘model’ to human condition*

Imutran have justified their use of primates by claiming that their immune systems are sufficiently similar to humans for the results gained in their experiments to be informative about the human situation. However, this is a debatable assumption. In one internal document, Imutran explicitly acknowledge a difference between the immune systems of baboons and human beings that is relevant to the processes of organ rejection.²⁵⁶

²⁵⁶ See File [REDACTED]

A meeting of scientists organised by the US regulatory body, the FDA, in June 1999, raised a series of points relevant to this issue, highlighting “dissimilar immunobiologies in non-human primates and in humans” and differences in the effects of immunosuppressant drugs between primates and humans that meant that the results gained in primates would not correspond to the outcome in human beings.²⁵⁷

- *“Likelihood of ‘success’”*

In 1995, Imutran claimed that they would be ready to commence clinical trials of xenotransplantation the following year. The imminence of clinical trials appears to have been put forward by Imutran in support of an application to conduct primate experiments. However, the profound and inscrutable biological obstacles to pig-to-human organ transplants have confounded significant progress. Five years later, in April 2000, Novartis have set Imutran an 18 month limit to achieve substantial progress in survival times and management of xenograft rejection. The improvements required appear to demand a quantum leap in progress, far surpassing that achieved in the previous five years at the cost of hundreds of primates lives, their severe suffering, and the lives of thousands of pigs.

In the meantime, Imutran have been publishing papers highlighting their longest survivors, while claiming that the primates tolerate the procedures and drug regimens well. We believe that the evidence presented here raises serious doubts about these assertions of ‘success’.

Furthermore, over a quarter of the primates vivisected have died as a result of technical failures in the surgical procedure. At least three more animals died as a result of complications arising from biopsies.

- *“How the data generated will be used”*

If the company reaches its survival targets, Imutran intend to submit the data generated from these studies in support of future applications to conduct xenotransplantation clinical trials, probably in the U.S.. However, as mentioned above, the company appears to be having “severe problems” with the condition of the data. This may be related to possible shortfalls in GLP referred to above.

- *“Utility of the product or substance being tested”*

We believe that the lack of progress in xenotransplantation research was entirely predictable, based on theoretical considerations. A full consideration

²⁵⁷ Meeting of the US FDA’s Biological Response Modifiers Advisory Committee Xenotransplant Subcommittee, held in Maryland on 4 June 1999.

of the insights of evolutionary biology and speciation²⁵⁸ leads us to conclude that the notion of successful pig-to-human organ transplantation is akin to alchemy. Pig organs have evolved over millions of years to function within the context of the porcine condition. Coupled with an acknowledgement of the virtually infinitely complex nature of biological organisms, especially animals, the fundamental argument against the notion of pig-to-human organ transplantation is compelling. On the immunological front, this position has been borne out by the outcome of Imutran's research. On the physiological front, research had refuted simplistic claims that similarities in size between pig and human organs makes the former suitable as replacements for the latter, and cast doubt on assertions that the physiology of pigs is sufficiently similar to humans to make xenotransplantation a viable option: as one researcher puts it – “a chain is as strong as its weakest link”.²⁵⁹

However, the most alarming consideration that undermines the utility of xenotransplantation is the danger of new viruses being introduced into the human population as stowaways in xenografts. Xenotransplantation is a uniquely efficient process for introducing new viruses into the human population. Particular concern has been expressed about porcine endogenous retroviruses (PERVs), which cannot be eliminated from pigs and are found in Imutran's transgenic pigs. Other, unknown viruses will inevitably exist. Furthermore, the unpredictability of viruses arising from their ability to rapidly mutate and recombine exacerbates the threat posed by them. The grave ramifications of this issue for public health are slowly being acknowledged by regulatory bodies around the world, and these persistent dangers appear to be one of the contributory factors towards Novartis' decision to set an 18 month time limit on the evaluation of xenotransplantation.

The *marginal* utility of xenotransplants (the most meaningful guide to its usefulness) is further eroded by the potential for a combination of health promotion, an expansion of the pool of human donor organs, and recent developments in mechanical devices to simultaneously reduce demand and increase the supply of treatment for organ failure.

8.2 Recommendations

Taking into account this discussion of the relevant features of the cost-benefit analysis, we suggest that xenotransplantation research should never have been licensed in the first place. The argument against the licensing of such research has grown in weight as the biological barriers and the potential public health hazards, as well as the extent of animal suffering have been confirmed in practice.

²⁵⁸ H LaFollette & N Shanks, *Brute Science: dilemmas of animal experimentation*, Routledge 1996: 72-160.

²⁵⁹ C Hammer, “Physiological obstacles after xenotransplantation”, *Annals of the New York Academy of Sciences* 1998 Dec 30;862:19-27. C Hammer, “Xenotransplantation: facts and fiction,” *Ann Chir Gynaecol* 1997;86(2):195-201. SJ Crick et al, “Anatomy of the pig heart: comparisons with normal human cardiac structure”, *Journal of Anatomy*, 1998 July; 193 (Pt 1): 105-19.

We therefore recommend that all licences to conduct xenotransplantation research on animals be revoked immediately, and we highlight the need for an independent judicial enquiry to examine the Home Office's initial decision to licence this research and their subsequent failure to halt it.

To sum up, these are our urgent recommendations:

- 1. The revocation of all licences to conduct xenotransplantation research on animals.**
- 2. A prohibition on the use of primates in research**
- 3. The revocation of Huntingdon Life Sciences' Certificate of Designation and rehoming of animals currently incarcerated therein.**
- 4. An investigation by the Good Laboratory Practice Monitoring Authority into the conduct of the whole research programme.**
- 5. Most importantly, an independent judicial enquiry should be instituted to investigate possible breaches of UK and European law that may have taken place during the course of this research; and the conduct of the Home Office throughout this whole affair.**

We believe that the issues raised in this report cast doubt on the commitment of the Home Office to regulate animal experimentation effectively. Not only does this have disturbing implications for the animals concerned, but it also calls into question the department's enforcement of the rule of law. Essentially, we would expect, at the very least, the Home Office to change and adopt the pro-active and rigorous approach that the law and the public demand. The trigger to such change is an independent enquiry into the entire affair. We suggest the following for the terms of reference for an independent judicial enquiry:

“To investigate the circumstances surrounding xenotransplantation research conducted on animals by Imutran Ltd in order to identify the lessons to be learnt regarding the ethics of animal experimentation and legislative and executive approaches to the matter.”