

**Comments Submitted to the National Health
and Medical Research Council, Canberra,
Australia on:**

**“Draft Guidelines for Clinical
Xenotransplant Research”**

September 6, 2002

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To whom it may concern,

The Campaign for Responsible Transplantation (CRT) is an international coalition of physicians, scientists and 90 public interest groups representing millions of people concerned about the public health risks inherent in xenotransplantation and the irresponsible rush to commercialize the technology.

CRT believes that xenotransplantation poses a grave danger to public health because of the risk of transferring potentially deadly zoonotic viruses to the human population. If it is developed further, xenotransplantation will also burden society with a host of complex regulatory, administrative, financial, legal, social, ethical, and environmental problems.¹ Despite this, the technology is receiving substantial public and private financing with virtually no public consultation.

CRT would like to comment on the National Health and Medical Research Council's (NHMRC's) "Draft Guidelines for Clinical Xenotransplant Research," issued 8 July, 2002.

PART 1

2.2 Why do we need to consider xenotransplantation?

"Do we really need xenotransplantation?"

Beauchamp G. Ethics and Xenotransplantation. *Canadian Journal of Surgery* February 1999; 42 (1): 5-6.

Although the NHMRC claims to want to facilitate a "vigorous public discussion" on xenotransplantation research," (p. xxxvi), it appears, from the substance of these guidelines,² and Dr. Kerry Breen's statements to the press,³ that the decision about whether or not to proceed with xenotransplantation has already been made. There is an inherent assumption that the public will embrace the technology. This is unethical and undemocratic, particularly since studies have revealed public unease about the technology⁴ and Australians have not been properly consulted. After a recent public consultation in Canada, a majority of citizens involved "voted" for a moratorium on clinical xenotransplant trials after learning of the risks.⁵

The question clearly needs to be reframed: ‘Should we consider xenotransplantation at all?’
CRT does not believe so for reasons that will be discussed below.

2.2.2 Burden of Disease and Demand for Transplants

“The primary aim of public health policy should be prevention.”

Allan JS. The Risk of Using Baboons as Transplant Donors: Exogenous and Endogenous Viruses. *Annals of the New York Academy of Sciences* 1998; 862: 95.

We are continually told that organ transplant waiting lists are growing. **This guideline states that “the demand for organs in developed countries is growing at 15% per year,” (p.15). But no one, including the NHMRC, seems to be asking why.** Why are more people getting diabetes, heart, liver, and lung disease; why are transplant waiting lists getting longer? And what can we do to *reverse* this unsustainable⁶ trend and *prevent* disease *before* it begins? The answers are readily available.

Binns and Leong write that, “cardiovascular disease shares common risk factors with other leading causes of death, including lifestyle behaviors (diet, physical inactivity, alcohol consumption, smoking), physiological states (obesity, hypertension, high blood cholesterol) and socioeconomic factors.” They say that in western countries, “of which Australia is a typical example, health promotion activities and improved hospital treatment have been effective in reducing the impact of the coronary heart disease epidemic.”⁷

Noted researchers like Dean Ornish have shown that lifestyle changes can reverse coronary artery disease,⁸ and save money.⁹

Smoking is the single largest cause of preventable disease and death in the world. Implementing proven smoking cessation interventions can reduce the risks of cancer, heart disease, and lung disease and save money.¹⁰ Similarly, avoidance of alcohol can prevent cirrhosis of the liver.

Felber and Golay state that “the relationship between obesity and type 2 diabetes has been known for decades and the recent increase in such diseases represents a major medical problem worldwide.” The authors state that lifestyle changes and weight loss programs can reverse obesity and potentially prevent diabetes.¹¹

A landmark study by Harvard University researchers, published in the *Annals of Internal Medicine* (Feb. 5, 2002) concluded that the risk of diabetes is increased nearly 60% by the Western diet, defined as high consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets.¹²

The American Diabetes Association has concluded that “there is now substantial evidence that type 2 diabetes can be prevented or delayed . . . [through] policies that focus on lifestyle modification,

specifically modest weight loss and increased physical activity. . . Public health messages, health care professionals, and health care systems should all encourage behavior changes to achieve a healthy lifestyle.”¹³ According to the U.S. Centers for Disease Control (CDC), each \$1 spent on diabetes outpatient education saves \$2 to \$3 in hospitalization costs.¹⁴

A paper entitled *Preventing Chronic Disease: A Strategic Framework (October 2001)* published by the Victoria Department of Human Services, and endorsed by the Australian Health Ministers’ Council in May 2001, describes the burden of chronic illness in Australia. The paper states that “preventive action on common risk factors [such as diet, obesity, physical activity and tobacco use] can . . . provide benefits across several diseases and conditions simultaneously.” The paper states that “effective action on prevention is, therefore, a high priority.”¹⁵

The NHMRC guideline makes absolutely no mention of this paper, or the important role of prevention in health maintenance - a glaring oversight.

NHMRC makes the unsubstantiated claim that alternatives to xenotransplantation “will not provide clinical solutions in the near future.” However, several research teams are using *human* cells to treat Parkinson’s and diabetes, most notably the Seattle Human Islet Transplantation Project and James Shapiro, et al., at the University of Alberta in Edmonton, Canada.¹⁶ Human cell lines are being developed for bioartificial liver devices because of concerns about xenozoonoses from porcine cells;¹⁷ and technology is advancing so rapidly, that the prospects for using human stem cells to treat diseases are quickly advancing.

Ariff Bongso and colleagues at ES Cell International, (an Australian-based company partly owned by the Singapore Government) have grown human embryonic stem cells using feeder layers from human muscle, skin, and fallopian tube, eliminating the risk of xenozoonosis.¹⁸

As the virtues of pig cellular transplants are extolled in this guideline (p.15), despite their potential dangers,¹⁹ virtually **every alternative to xenotransplantation is discredited through the use of defeatist language (pp.16-17):**

- “even if it [presumed consent] were . . . ethically acceptable, . . . would not overcome these difficulties;”
- “. . .but . . . this option [hospital procedures] is unlikely to greatly reduce the length of waiting lists;”
- “But creating a market for human organs . . . is considered to be ethically unacceptable . . .;”
- “However, the production of . . . mechanical alternatives. . . is probably some decades away;”
- “. . .there are still many hurdles that must be overcome [to grow organs in test tubes];”
- “[S]tem cell technology cannot be regarded as an ‘alternative’ to xenotransplantation because current stem cell lines are grown on animal feeder layers. . .” [no longer true]

Such defeatist language should be eliminated from the guideline. There is no evidence that xenotransplantation will provide solutions in the near future, given its poor track record. It remains a highly experimental, risky, costly and inhumane technology, which has not been widely endorsed by the public or the medical community. The NHMRC guideline does not reflect this reality.

2.2.3 Alternative sources of organs and tissues

The guideline cites the low organ donation rate in Australia as a justification for considering xenotransplantation. But CRT does not believe that countries are doing enough to increase human organ donation. Even in the U.S., where 85% of the populace supports organ donation, less than 40% become donors;²⁰ and **studies show that many more organs are available than are being accessed through existing organ procurement efforts.**²¹

Similarly, although some 60% of Australians support organ donation, only 26% of suitable potential donors actually become donors. Pearson and Chapman, who promote an in-hospital computerized organ donor index to track and audit individual hospitals' performance in organ procurement,²² write that data are lacking on the possible reasons for poor donor rates.^{23 24}

Gullifer and Gill (1997) suggest that further research is needed to:

- Ascertain the Australian public's knowledge about organ transplantation;
- Ascertain the Australian public's perception towards organ transplantation;
- Determine the number of people who refuse a request to donate viable organs;
- Ascertain why potential donors or next of kin refuse requests;
- Ascertain the Australian public's views towards presumed consent,²⁵ monetary rewarding, and required consent;
- Determine if Australians would be receptive to appeals to altruism with respect to donation of their organs;
- Determine if cultural background and religious affiliation influence one's views toward organ transplantation; and
- Determine the effectiveness of education campaigns directed toward the public and healthcare personnel.²⁶

Launching national print, radio, and television education campaigns aimed at increasing human organ donation could be considered or improved.

Enhancing communication strategies among transplant centers and organ procurement organizations, and re-training hospital staff to improve communication with grieving families has been identified as vital in numerous studies.²⁷ One study suggested instituting nationally standardized hospital procedures to ensure that all potential donors are identified, and that every family is respectfully approached about the possibility of organ donation.²⁸

Other suggestions have included: expanding the donor criteria to include older donors,²⁹ increasing recovery of organs from non-heart beating donors,³⁰ and re-evaluating the criteria for brain death.³¹ A study in the January 22, 1998 issue of the *New England Journal of Medicine*, reported that cadaveric organ donation - using kidneys from newly deceased people whose hearts have stopped beating - could increase the supply of kidneys two-to-five fold.

Split organ transplants of livers from cadaveric donors could save two lives instead of one and reduce the number of people on liver transplant waiting lists.³² Multiorgan procurements (where in addition to the kidneys, at least one other organ is procured) is practiced in the Slovak Republic, and represents almost 80% of the total number of cadaveric procurements.³³

Some surgeons have proposed surgical techniques, such as ventricular remodeling, to avert transplantation. About 75% of patients who undergo this procedure - in which a section of heart muscle is removed and reshaped - can be taken off the transplant waiting list.³⁴

The NHMRC should analyze and evaluate all of these issues and possibilities fully, and discuss them in public consultations, before proceeding to a new draft of this guideline.

2.3.1 and 8.1 – 8.5 Animal Welfare Concerns / Efficacy and Ethics of Pig-to-Primate Experiments

“Keeps holding area where transplanted heart is . . . Quiet and huddled . . . Reluctant to move. Marked firm swelling around implant. Animal showing obvious discomfort. . . Sero-sanguinous fluid drained. . . Swelling so large animal sacrificed for humane reasons.”

Baboon W250m, who died in a Novartis study involving the transplantation of transgenic pig hearts into the necks of wild-caught baboons. From a cache of leaked documents. Draft UK Xenotransplantation Report, 2000, p.5.

This guideline fails to minimally address the serious animal welfare concerns inherent in xenotransplantation, and fails to mention the extreme suffering endured by animals, particularly higher primates, involved in xenotransplantation research.

In xenotransplantation pre-clinical research, nonhuman primates, such as baboons and cynomolgus monkeys, have had organs from pigs and other primates grafted into their necks and stomachs. None have survived longer than days or weeks; many have died from infections and/or poisoning from the toxicity of immunosuppressive drugs. CRT believes that such suffering is unjustifiable and should not be condoned by the NHMRC.

Developing transgenic pig herds for xenotransplantation research also involves much suffering. “Many inherently distressing processes are involved including genetic engineering, cloning, reproductive manipulations,³⁵ surgical operations, the separation of sows and piglets, close confinement in unnatural indoor conditions, and invasive health status monitoring.”³⁶

Because genetic engineering techniques are imprecise, it is unknown how many thousands of animals may be bred and killed as by-products because they do not carry the genetic trait(s) desired by a company.³⁷

British reporter Anthony Browne writes that, in order to obtain pig cells to treat Parkinson's Disease patients, "pregnant genetically modified sows are slaughtered, their foetuses are chopped out, their heads cut off, and their brain cells sucked out and injected into the heads of humans."³⁸ For a single transplantation of pig pancreatic islet cells into a diabetic patient, 39-100 fetuses (4-8 litters) may be used.³⁹ Since tens of millions⁴⁰ and often billions of cells are required for some of these treatments,⁴¹ such a wholesale slaughter of sows and young piglets would become the norm if xenotransplantation were to become widely adopted.

Pigs raised for xenotransplants spend their entire lives in sterile, confined areas with no exposure to grass or sunlight. Overcrowding leads to stress, vicious fighting and cannibalism.⁴² It is difficult to understand how the NHMRC will assure that source animals are healthy and "treated humanely," particularly if their care is entrusted to the very companies who seek to exploit them (section 8.4.2), and since the animals will be subjected to genetic manipulations and surgeries which are inherently inhumane. "Overseas" operations (section 8.5.2) will be virtually impossible to monitor.

Data derived from Dolly the sheep and other cloned and transgenic animals have revealed that such animals often have weaker immune systems, and may be born with physical disabilities which cause them great pain, such as chronic arthritis, swelling of joints, enlarged organs, blindness and respiratory ailments.⁴³

Recently published studies in the *Journal of Cloning and Stem Cells*, cite a high mortality rate for cloned piglets at two American universities. They document deaths and deformities, including heart failure, lameness, and anemia. Texas A & M University documented a 94% failure rate. Only 28 of 511 manipulated embryos came to term; one was stillborn, another was born without an anus or a tail.⁴⁴

Cloning pigs will not rid the animals of the numerous viruses, bacteria, and parasites they carry, including the Porcine Endogenous Retroviruses (PERVs) (see below).

Efficacy and Ethics of Pig-to-Primate Experiments

"What disturbs me is this tacit assumption that continues on this board, that these animal models are appropriate models for the human transplant, so that we talk about appropriate expectations of success. . . The question is have you . . . pushed the animal model. . . past the limit that is reasonable?"

Dan Salomon, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.48 in transcript).

"There is a lot of money going down that road right now . . . I mean is the biology in the non-human primate the same [as a human]? No, it is not."

Dan Salomon, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.39 in transcript).

“Everybody agrees that there are limitations to various degrees in pig to baboon, or pig to non-human primate in general. . . . Has anybody got a better model?”

Hugh Auchincloss, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.50 in transcript).

There are a couple of challenges in these baboon models . . . there are going to be differences between the baboon and the human.”

Marlin Levy, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.23 in transcript).

“. . .the limitation of the preclinical model that we are forced to use today in our laboratories.”

Emanuele Cozzi, M.D., Imutran, speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.31 in transcript).

It is disheartening that the NHMRC guideline calls for more gruesome pig-to-primate experiments to be conducted in Australia. They should not proceed. Hundreds of these experiments have already been performed,⁴⁵ and are ongoing around the world with dubious outcomes.⁴⁶ Researchers have acknowledged that such experiments may not provide information relevant to the safety or efficacy of xenotransplantation in humans, and that nonhuman primates are poor models for humans (see enclosed U.S. FDA meeting report, June 4, 1999).⁴⁷

In September 2000, internal documents, leaked from the Swiss multinational Novartis AG Pharma - a primary investor in xenotransplantation - revealed glaring technical failures and horrific animal suffering in pig-to-primate experiments sponsored by the company and its (now defunct) British subsidiary, Imutran, Ltd.. Dan Lyons of Uncaged Campaigns, the British advocacy group which received the extensive caché of **leaked documents** from an anonymous source, published a report entitled, *Diaries of Despair: The Secret History of Pig-to-Primate Organ Transplant Experiments, a draft of which is enclosed here.*⁴⁸ **We urge the NHMRC Committee to read it.**

Among the leaked documents, were 39 draft study reports describing pig-to-primate experiments commissioned by Imutran and conducted by the controversial contract research laboratory, Huntingdon Life Sciences, in Cambridgeshire.

The documents revealed: a failure to overcome the intrinsic biological obstacles to xenotransplantation, despite headlines to the contrary; inadequate Government regulation; incompetence in the conduct of research; and severe animal suffering endured by higher primates (recorded by the researchers themselves).

In the experiments, juvenile baboons and cynomolgus monkeys were transplanted with genetically engineered piglet hearts and kidneys: over a quarter of the primates died as a result of the surgery. The survivors were heavily dosed with cocktails of toxic anti-rejection drugs, but died from complications related to drug side-effects, infection, rejection, hemorrhage, and organ failure, most within hours or days

of their surgeries. Diarrhea, vomiting, tremors, weakness, swelling of the eyes, wounds seeping blood and pus, rapid involuntary eye movements, breathing difficulties, and grinding of teeth - were some of the recorded list of agonies these animals endured.

Documents suggested that 473 higher primates were killed in Imutran's xenotransplantation research program; though Uncaged uncovered evidence that another 160 primates, including 80 wild-caught baboons, were killed in a 1995 research program involving the transplantation of hearts from cynomolgus monkeys into the necks of baboons.

In one shipment of cynomolgus monkeys to Imutran in August 1998, three animals were found dead with blood seeping from their nostrils after an arduous voyage of 48 hours. Welfare experts suggest that their crates were poorly ventilated and too small for the monkeys to turn around and lie down in.

At least 520 errors and omissions in the conduct of pig-to-primate studies were noted in the documents, including organ weights not recorded, unlabelled and uncovered veterinary medications, inadequate surgery records, a quadruple overdose, the illegal re-use of animals, conflicting pathology reports, the accidental freezing of a kidney during transplantation surgery, and the leaving of a swab inside a primate which resulted in his death. Seven baboons in one study appeared to have been experimented upon despite a warning that they "must not be worked on due to positivity for Herpes B."

According to Lyons, the documents demonstrate that, after five years of research, Imutran improved the average survival time of monkeys with functioning pig kidneys from just two to four weeks. The "success" rate of heart xenotransplantation was even less tangible, with the average survival being eleven days. Lyons suggests that Imutran only published a fraction of the data it collected and thereby exaggerated the level of preclinical "success" it obtained.

It is shocking that such negligent and unethical research was condoned by Novartis, a multinational company with \$32 billion in assets,⁴⁹ and the primary corporate investor in xenotransplantation research. Given the secretive nature of this research, and the fact that smaller companies have fewer resources at their disposal than Novartis, it is likely that such abuses and transgressions are the norm rather than the exception in xenotransplantation laboratories.

Pig-to-primate experiments should not be conducted in Australia, or contracted out by the government, or condoned by the NHMRC.

3. Ethical and Social Issues

Readers of the Uncaged report will realize that animal-based xenotransplantation research can never be "humane and reasonable" (p.27), that it cannot meet any standards for "humane stewardship for living creatures," (p.26), and that it is, in fact, the cause of "unnecessary suffering," (p.27).

The notion that animals can be reared and killed humanely for food⁵⁰ or xenotransplantation is either naïve or absurd. Books like *Slaughterhouse: The Shocking Story of Greed, Neglect and Inhumane*

Treatment Inside the U.S. Meat Industry by Gail Eisnitz (Prometheus Books, 1997), lay the concept of “humane killing” to rest.⁵¹

Environmental Concerns

What environmental impact will transgenic pig breeding facilities have on local communities? Though these concerns are rarely, if ever, raised in the context of xenotransplantation, they are relevant and important and **should be addressed by the NHMRC.**

This guideline states (p. 108) that “animal products and byproducts not used in xenotransplantation are disposed of by appropriate methods,” though these are not explained.

The adverse environmental and health impacts of animal-based agriculture have been well-documented (see www.hogwatch.org and www.sierraclub.org/factoryfarms/rapsheets).⁵²

Many experts have addressed the problem of farm animal carcass and waste disposal and have stated that "the use or disposal of animal wastes directly impacts the quality of the land and water." Others say that "improper disposal of dead animals can result in surface water or groundwater contamination." Hundreds of hog manure lagoons, needed as part of hog productions in large factory farms, are leaking contaminants such as nitrates - chemicals linked to "blue baby syndrome" - into the groundwater. Pathogenic water-borne organisms in manure include Salmonella, listeria, vibrio, brucella, cryptosporidium, coxiella, chlamydia, and mycoplasma. Pesticides and insecticides (commonly used in agriculture), and their by-products may also contribute to soil and groundwater contamination.

How will facilities breeding pigs for xenotransplants deal with the thousands of tons of manure generated by their facilities? And how will they, and/or hospitals, dispose of remains of thousands of genetically modified animals and their offspring once their organs have been harvested? Conventional agricultural operations and rendering plants continuously wrestle with the problem of how to dispose of millions of tons of perishable animal tissue each year. Incineration, burial, and composting have all been described as expensive, unhygienic, and environmentally problematic options. In his 1996 report for Sandoz, ‘The Unrecognized Potential of Xenotransplantation,’ (p.40), Peter Laing of Salomon Brothers UK suggested that the remains of transgenic pigs could be “usable as pet food.” Could transgenic pigs find their way into the human food chain, either by being fed to other farm animals, (as chicken remains are now fed to pigs), or might they be processed for human consumption?⁵³

3.3.1 Research involving humans.

- **How xenotransplantation serves the common good**, particularly given its potential to unleash an AIDS-like epidemic on an unsuspecting public, **remains unclear and has not been explained in this guideline.**
- The therapeutic potential of xenotransplantation has yet to be demonstrated.
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- In CRT’s opinion, the alleged benefits of xenotransplantation, which have yet to be demonstrated, do not justify its significant risks (see Section 6 below).
- In CRT’s opinion, xenotransplantation does indeed expose participants, close contacts and society to unreasonable risks.
- In 1994, three out of four patients who underwent an ex-vivo pig liver perfusion, at the Duke University Medical Center in North Carolina, died. They were too ill to give their informed consent, so it was obtained from their next of kin⁵⁴ (relevant to section 7.2.2). The researchers were never reprimanded; one, Jeffrey Platt, now runs the xenotransplant research program at the Mayo Clinic in Minnesota which receives funding from Baxter Pharmaceuticals⁵⁵

Today, many investigators are affiliated with corporate sponsors. According to the *Washington Post Magazine*, “today 80 percent of clinical trials are funded by private industry, not by government” (this is a concern for section 9.3.1). In the U.S., adverse events in clinical trials are classified as “confidential commercial information,”⁵⁶ something CRT is currently fighting.⁵⁷ In other words, the public does not have the right to know about them. So the integrity and safety of research, how it is evaluated, by whom, and the claims made by its proponents, should certainly be scrutinized by independent observers.

3.4.1 Allocation of resources/funding

“This will be extraordinarily unimaginably expensive, and to forget that for a moment, I think is inappropriate . . .”
Robert Michler, M.D. speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.14 in transcript).

In 1996, the Organisation for Economic Cooperation and Development (OECD) stated that “[t]he economic impacts of the development of xenotransplantation have not been adequately addressed.”⁵⁸ That is still true today.

Obviously, the **NHMRC has not prepared a cost-benefit analysis** to determine the true cost of xenotransplant procedures and the economic impact the widespread application of the technology, and any zoonotic pandemic, would have on Australia’s health care system (p.31). This seems like economic suicide.

Xenotransplantation promises to be even more expensive than allotransplantation. In addition to the operations themselves, there are hidden costs of: housing, breeding, feeding, medicating, testing, and disposing of the remains of herds of transgenic animals; of hiring skilled hospital personnel, surgical staff, infectious disease experts and veterinarians capable of properly monitoring xenograft patients, their close contacts and source animals; of government-mandated patient registries, blood and tissue archives, programs and technologies to screen for new viruses, and unpredictable medical and legal costs associated with disease outbreaks.

Who would absorb these costs? Who would pay for the procedures themselves and the expensive drug regimens? Industry, which has invested hundreds of millions of dollars to breed transgenic pigs and fund clinical trials, hopes that governments will. This will inevitably drive up health care costs for all Australians.

Containment, screening and treatment for infectious diseases are extremely costly for governments. AIDS treatment and prevention is costing governments billions. Add to that, fees for hospital stays, doctor visits, and blood tests. The hundreds of millions of federal dollars spent on AIDS research, including hundreds of millions allocated to develop a vaccine, should also be tallied; such increased spending is an inevitable consequence of an epidemic. Is the Australian government prepared to pay for this?

In addition, a xenogeneic infection in the human population could reduce the number of available human organs for transplantation, driving costs for human organ transplants even higher.

Rather than state that all the costs involved with xenotransplantation ‘cannot be predicted’ (p.31), **the NHMRC would do well to confront these issues now. It may realize that xenotransplantation is not economically feasible.**

4. Scientific and Technical Issues

CRT found this section overly technical and pointless for most laypersons.

We were disappointed by exaggerated statements not supported by any documentation, like: “there appear to be no insurmountable physiological barriers to the use of pig hearts and kidneys,” (p.36). Such statements reveal a blatant disrespect for the complexity of biological systems; they are contradicted by numerous studies⁵⁹ and by real life experience. Since 1905, 82 humans have received whole organs from chimpanzees, baboons, pigs, goats and other animals, and a majority have died from infections and complications related to hyperacute rejection within hours or days of their surgeries.⁶⁰

PART 2

5. Will xenotransplantation work?

“We have had no clear long-term human successes.”

Robert Michler, M.D. speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.11 in transcript).

“Data so far... indicate that the survival of xenografts is expected to be much shorter than that of allografts. Given these considerations, do the potential benefits . . . outweigh the potential risks?”

Louis Marzella, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.34 in transcript).

“They [patients] are going to be getting a lot of drugs, more drug than they would have needed for an allotransplant. There are a variety of reasons why the patient will be in worse condition.”

David Sachs, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.48 in transcript).

“Is there anybody who thinks that it is time to be thinking seriously about pig livers or pig lungs, or any other solid organ? No.

Hugh Auchincloss, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.50 in transcript).

“To my knowledge, the only time that a xenoliver has been attempted as a true bridge, it was a dismal failure.”

David Sachs, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.49 in transcript).

“The science for this [xeno] is we have a dead-end, it looks [like] a dead-end street we are driving down.”

Harold Vanderpool, PhD, speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.54 in transcript).

“..the challenge [is] in maintaining these animals in a healthy state when one is performing invasive technologies...”

John Logan, Nextran, speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.18 in transcript).

“...the maximum duration of survival in animal recipients of life-sustaining cardiac transplants is only measured in weeks. As we have heard, significant technical obstacles, such as requirement for repeated invasive monitoring and invasive therapeutic interventions interfere with the ability to fully assess the potential risks and benefits of xenotransplants.”

Louis Marzella, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.36 in transcript).

Cooper: “So your clinically applicable dosages of immunosuppression are not controlling the rejection, but are actually, in that animal [monkey], over-immunosuppressing to the point that they are getting tumor formation.. .

Cozzi: “There are some stages where we are obliged to give up the immunosuppression or reduce the draws . . . because the animal is sick and unwell. . .So. ..yes, we have lymphoproliferative disorders, possibly . . acute vascular rejection in that animal.”

David Cooper, M.D. and Emanuele Cozzi, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.42 in transcript).

Woodle: “[Y]ou don’t have the first idea of how you are in the Stone Age with an animal in the laboratory.”

Steve Woodle, M.D., speaking at a meeting of the FDA Xenotransplant Subcommittee, June 4, 1999, (p.45 in transcript).

It is clear from the above quotes, the two documents that CRT has enclosed with its submission,⁶¹ and from the poor survival outcomes described in section 5 of this guideline, **that the animal-to-animal models⁶² are not providing useful criteria with which to measure clinical xenotransplantation outcomes.**

Numerous factors call the utility of these studies into question: complex species differences between nonhuman primates and human beings, the invasive nature of the experimental protocols themselves which impair the collection of meaningful data,⁶³ and the fact that these studies cannot assess risk.

With respect to clinical xenotransplant trials, the data in this chapter are vague. Numbers of patients in trials are missing (i.e. pp.56-57), making it difficult to assess claims of benefit. A trial that includes one or two patients, for example, is much less significant than one that includes 50-100 patients.

The few improvements recorded in a handful of cellular xenotransplant experiments (i.e. for Parkinson's disease) (pp.55-56) could well be the result of a strong placebo effect. Last year, Canadian researchers found that Parkinson's patients given a placebo saline injection showed a significant rise in dopamine levels in the brain. Apparently, the mere anticipation of an effect may create an effect of its own.⁶⁴

CRT hopes that clinical xenotransplant trials do not go ahead in Australia, but should they proceed, it would be unwise, given the profits at stake, for the NHMRC to allow sponsors to assess the outcomes of their own clinical trials (section 5.6.3).

(P.S. Bailey et al transplanted a baboon heart into a newborn baby in 1984, not 1982.)

6. Is xenotransplantation safe?

"[We] are preparing a new infectious Chernobyl."

Chastel CE. The Dilemma of Xenotransplantation. *Emerging Infectious Diseases* April-June 1996; 2 (2): Letters.

"[T]he risk of viral transmission from swine to human appears substantial."

Borie DC, et al. *Infection Control and Hospital Epidemiology* May 1998; 19 (5): 357.

"[O]ur understanding of the retrovirology of xenotransplant source animals is incomplete . . . little or nothing is known about the pathogenic potential of endogenous retroviruses introduced directly into other species."

Stoye JP, et al. Endogenous Retroviruses: A Potential Problem for Xenotransplantation. *Annals of the New York Academy of Sciences* 1998; 862: 68.

". . .the real issue is that the viruses that we really need to worry about are certainly new viruses that could. . . have a very big impact . . . on the pig population and have a very long latent period in people, those are the viruses we need to worry about and, by definition, we don't know what they are."

David Onions, PhD, virologist, speaking at a meeting of the FDA Xenotransplant Subcommittee, June 3, 1999, (transcript, p.66)

"[T]ransplanting an organ carrying endogenous xenotropic provirus is equivalent to injecting a patient with live C-type virus. . . . to casually ignore its virtual certain presence in transplant trials makes little sense."

Stoye JP, Coffin JM. The Dangers of Xenotransplantation. *Nature Medicine* November 1995; 1 (11): 1100.

“Even if the risk of producing a “new infection” were as low as one in 1000 there could be at least 10 infections each year. Any one of these outbreaks could become a major public health problem with the potential for intercontinental spread.”

Collignon PJ. Xenotransplantation: Do the Risks Outweigh the Benefits? *Medical Journal of Australia* 18 May 1998; 168: 519.

Similarly to the U.S. guideline, this guideline lays out the infection risks associated with xenotransplantation. The NHMRC appears to recognize that pigs pose as great of a concern as nonhuman primates as source animals.

Indeed, numerous documents enclosed with this submission, and cited in this guideline, describe the clinical threat posed by porcine diseases in the context of xenotransplantation, most notably an article by Dominic Borie and colleagues⁶⁵ who suggest possible transmission of porcine viruses, such as pseudorabies, to human recipients of porcine islet cells.⁶⁶ Borie, et al., write that, in the context of xenotransplantation:

- Bacteria could theoretically be transmitted to humans in the event of bacteremia, occurring during organ harvesting. Current procedures of organ preservation before grafting would not necessarily circumvent the risk because bacterial growth at temperatures close to 0°C has been documented for bacteria like *Yersinia*. Detection of bacteria with current assays may prove difficult.
- In humans, liver abscesses caused by *Entamoeba histolytica*, and gastrointestinal infection by *Entamoeba polecki*, commonly found in pigs, have been documented. Pig organs may be infested with parasites. Such parasites may not currently be recognized as zoonoses and might become established in immunosuppressed patients.
- Numerous fungal infections, in humans and pigs, are latent in healthy individuals, but may become activated after host defenses are weakened by immunosuppression.
- Pigs carry a broad spectrum of potentially zoonotic viruses which cause a wide range of symptoms in humans, including fever and general malaise, sores on the face or feet, neurological disorders, meningitis, and death.

It is estimated that hundreds of different endogenous retroviruses may be present in one animal.⁶⁷ Viruses infecting pigs that cannot be guaranteed to be absent from a xenograft include porcine retrovirus, porcine polyomavirus, porcine parvovirus, porcine circovirus, porcine cytomegalovirus, porcine reproductive and respiratory syndrome virus, influenza virus, porcine hepatitis E virus,⁶⁸ and porcine herpesvirus.⁶⁹

In pigs, the expression of retroviruses has been associated with the development of leukemia and lymphoma.⁷⁰ In humans, retroviruses can induce chronic, life-long infections, “long latency malignancies, neurological disorders, wasting diseases and immunodeficiencies, for which treatment is

limited or unavailable.”⁷¹ Some retroviruses, such as simian foamy virus (SFV) and simian immunodeficiency virus (SIV), have spread to animal handlers with occupational exposures to baboons and rhesus monkeys, proving that transmission of retroviruses can occur under conditions that are less intimate than xenotransplantation.⁷²

Xenotransplantation poses inherent disease risks to patients and non-patients alike. Non-patients include animal handlers, surgical team members who harvest and implant animal organs, lab workers handling clinical specimens from xenotransplant recipients, nurses⁷³ and others who would provide medical care to the patient(s), relatives and friends of the patient, and the public at large.

Numerous studies have demonstrated the infectivity of a variety of human cells by porcine endogenous retroviruses (PERVs).⁷⁴ PERVs’ replication capacity has been found to *increase* when it is passaged in human kidney cells.⁷⁵

All pigs harbor type C endogenous retroviruses. Most cell lines derived from porcine tissues actively produce type C retroviruses;⁷⁶ novel type C PERVs are continually being discovered.⁷⁷ At least two infectious variants of porcine endogenous proviruses, (PERV A and B), are widely distributed in different organs, cells and tissues (spleen, heart, kidney, liver, lung, thymus) of different breeds of pigs. These retroviruses are passed from mother to offspring and therefore cannot be eliminated by the conventional techniques used to generate specific pathogen-free animals.⁷⁸ Indeed, although Oldmixon et al (2002) (aka Biotransplant) claim that they have bred a line of transgenic miniature pigs that do not secrete PERV (pp.71, and 73 of this guideline), PERV is still present in the pigs’ DNA. **This should be noted in the guideline.**

More importantly, veterinarian Michael Swindle asserts that “it will be impossible to provide complete individual animal screening in a timely fashion prior to performing a xenograft transplant.”⁷⁹

Therefore, all recipients of porcine cells, tissue, or organs would be exposed to PERVs and possibly other infectious organisms.

The greatest danger would come from something causing disease with a very long latency period. The transmissible spongiform encephalopathies, implicated in “mad cow disease” had very long incubation periods. The risks of transmissibility to humans were considered “remote.”⁸⁰

HIV-1 was transmitted silently from human to human until it was recognized as a causative agent for AIDS in the early 1980s.

Tacke, Kurth, and Denner (2000) have indicated that high titer replication of PERVs in transplant recipients could lead to an immunodeficiency disease, [similar to AIDS].⁸¹

Some researchers who are conducting⁸² or reviewing⁸³ clinical xenotransplant trials insist that xenograft patients tested for PERV have produced antibodies to the virus but no sign of clinical infection.

But noted virologists caution that, “the presence of antibodies may mean the virus has gone underground but it almost certainly means it [is] replicating.”⁸⁴

Researchers at Diatranz, New Zealand who have implanted encapsulated porcine islet cells into the abdomens of children in Mexico (where there are inadequate regulatory controls in place for such experiments) admit that pig islets contain PERV RNA and DNA. But they claim that PERV does not traverse the capsules. In 1999, xenotransplant researcher Hugh Auchincloss stated, “I cannot imagine an encapsulation technology that would convince me that no virus could possibly escape. . .”⁸⁵

PERVs are not the only viruses of concern. The swine influenza of 1918 killed 20-40 million people worldwide.⁸⁶ Influenza kills 20,000 and hospitalizes about 100,000 people in the U.S. annually,⁸⁷ and new strains of swine influenza are emerging.⁸⁸ A new report shows that U.S. farm workers are continually exposed to influenza.⁸⁹ The U.S. CDC projects that the next pandemic could kill between 89,000 and 207,000 people and result in up to 734,000 hospitalizations.⁹⁰ A flu epidemic recently killed some 300 people in Madagascar. The strain responsible is the H3N2 virus – [a human/swine/avian reassortment virus].⁹¹ Pigs act as mixing vessels for viruses from humans, birds and other mammals. Genetic reassortment in pigs could produce novel influenza strains with pandemic potential.

Another novel virus, the “Nipah” virus, was responsible for an encephalitis outbreak in Malaysia between 1998 and 1999 that infected 300,⁹² killed over 100, and led to the mass slaughter of some one million pigs and thousands of dogs, goats and sheep.⁹³ This virus jumped from fruit bats to pigs to humans and is a recently discovered member of the paramyxovirus family of viruses.

Another “Nipah-like” virus has been blamed for a neurological disease outbreak which infected 29 people and killed 9 in Bangladesh in 2001.⁹⁴ The “Menangle” paramyxovirus infected two piggery workers in 1997, causing flu-like symptoms.⁹⁵

Infectious diseases kill an estimated 52 million people worldwide.⁹⁶ Within the last 30 years, zoonotic agents have been transmitted to humans, resulting in subsequent human-to-human transmission. These include AIDS,⁹⁷ swine influenza, Marburg filovirus, Ebola virus, and new variant Creutzfeldt-Jakob (the human form of “mad cow”) disease.

Pigs likely carry many more viruses that have yet to be identified. American virologist Jonathan Allan has noted that it is impossible to screen for viruses that have yet to be discovered and says, “[s]eldom, if ever, have we had as much knowledge to prevent a future epidemic. What is lacking is the wisdom to act upon that knowledge.”⁹⁸

The NHMRC ought to admit to the public that xenotransplantation is inherently unsafe.

6.5 Managing the risks

While the real implications of possible harm to people are recognized in this guideline, the conclusion seems to be that clinical trials should proceed, with “appropriate safeguards” in place to “limit the infectious risk to the community.” But **risks cannot always be “managed;”** and from a reading of

Section 9, it does not appear that Australia has a clear set of laws in place to regulate xenotransplantation. Moreover, healthcare and regulatory systems are ill-prepared to deal with pandemics.

Identifying, treating, and controlling emerging infectious diseases and pathogens have created enormous challenges. The WHO *World Health Report, 1996*, states that, despite the emergence of some 30 new infectious diseases in the last 20 years, “there is still a lack of national and international political will and resources to develop and support the systems necessary to detect them and stop their spread. Without doubt, diseases as yet unknown but with the potential to be the AIDS of tomorrow, lurk in the shadows.”⁹⁹

Xenotransplantation trials have been ongoing in the U.S. for over a decade, without adequate safeguards.¹⁰⁰ CRT has published numerous reports and press releases (see enclosed) regarding FDA’s poor oversight of xenotransplantation, the blood supply,¹⁰¹ of human tissues infected with HIV and other viruses,¹⁰² of tracking and recall systems for defective medical devices,¹⁰³ and medical implants. **These findings should be of great concern to the NHMRC, since the U.S. is often viewed as a model for other countries to follow.**

This guideline recommends “adherence to current hospital infection control measures” (p.75).

Unfortunately, infection rates in hospitals are soaring. In the U.S. they are now the 4th leading cause of (preventable) death. Deaths from infections caused by unsanitary facilities, germ-laden instruments, and unwashed hands in U.S. hospitals rose to 103,000 in the year 2000, 14% higher than government estimates; 75% of those deaths could have been prevented.¹⁰⁴

Similarly, the Australian Health Care Study revealed high levels of adverse events in healthcare. The major categories of human error, accounting for 70% of adverse events were: 1) Failures in technical performance; 2) Failure to act on available information; 3) Failure to investigate or consult; and 4) A lack of care or failure to attend.¹⁰⁵

Clearly, our hospitals are ill-equipped to deal with the most basic infection control, patient care, and technical procedures. Now they are faced with the specter of bioterrorism preparedness in a time of staff and budget shortfalls. Add xenotransplantation and human error to the mix and it will be a recipe for disaster.

Risk Assessment

Traditional risk assessment and risk management approaches are not likely to be useful for xenotransplantation because nature and human behavior do not conform to a linear model: viruses do not behave in predictable ways, nor do sick people (see section 7.2.2, p.82). Moreover, what does

“acceptable risk” mean? As one member of a U.S. xenotransplantation committee said: “[H]ealthy people interpret [risk] much differently than sick people. To healthy people, any risk is unacceptable. . . on the other hand, a person who is dying of heart disease or liver failure is going to take any risk. So risk is very relative. Until anyone here can promise me that there is no risk, the general healthy public is going to say that they . . . don’t want to be exposed [to xenotransplant recipients]. That, I think is the bottom line, because if anything goes wrong, [the government] is going to be blamed for having caused a major disease.”¹⁰⁶

The Precautionary Principle

CRT believes that, if the NHMRC was truly interested in protecting the public from new infectious diseases it would ban xenografts, period.

As a government agency with a mandate to “raise the standard of individual and public health throughout Australia,” the NHMRC should honor the Precautionary Principle. The Precautionary Principle has been defined and incorporated into numerous international charters including the World Charter for Nature (1982), the Economic Summit of Industrialized Nations (1990), the Hague Recommendation on International Environmental Law (1991), Agenda 21 (Rio, 1992), and the Convention on Biological Diversity (1992), among others.

It instructs that:

- 1) People have a duty to take anticipatory action to prevent harm. When an activity poses threats to human health or the environment, precautionary measures should be taken to avoid that risk, even if some cause and effect relationships are not fully established scientifically. “This challenges the view that, until there is evidence that a new technology is harmful, it is acceptable to proceed with its development.”¹⁰⁷
- 2) The burden of proof of harmlessness of a new technology, process, or activity lies with its proponents, not with the general public. Taxpayers should not have to pay for the development of xenotransplantation, nor should they pay to assess its safety.
- 3) Before using a new and potentially dangerous technology, process, or activity, those with decision-making authority have an obligation to examine a full range of non-harmful alternatives, including the alternative of doing nothing.
- 4) Some technologies pose too great a risk and should simply not be pursued. CRT believes that xenotransplantation falls into this category.
- 5) Decisions applying the precautionary principle must be open, informed and democratic and must include affected parties.¹⁰⁸

CRT recommends that NHMRC discuss the Precautionary Principle in public consultations and devote a section to it in any future drafts of this guideline.

Conclusion

In general, this guideline raises some valid concerns about a range of issues, including safety, then proceeds to ignore them by proposing guidelines for clinical trials. It contains contradictory assertions¹⁰⁹ and assumptions, and it suffers from a lack of analysis in key areas such as:

- a) disease prevention,
- b) alternatives to xenotransplantation,
- c) the true economic costs associated with implementation of xeno in Australia,
- d) a detailed public health plan, including national procedures for a contagious infection, and
- e) a serious examination of the suffering endured by animals used in xenotransplantation research.

CRT believes that the NHMRC must place a hold on the development of these guidelines until it has conducted extensive public consultations.

Before considering a technology as extreme, dangerous, expensive and inhumane as xenotransplantation, the NHMRC should:

- Review the findings contained in *Preventing Chronic Disease* (see enclosed), which states that “effective action on prevention is . . . a high priority.”
- Based on the findings in the above report and in the medical literature, launch health promotion policies to reduce the incidence of chronic organ disease in Australia, thereby reducing the number of people on transplant waiting lists.
- Exhaust all avenues for increasing the supply of human organs.
- Fully examine, and allocate resources to, the range of available alternatives to xenotransplantation.
- Include the public in every stage of the decision-making process, through public forums, community meetings, frequent polling, and the like, and be honest about the risks and problems inherent in xenotransplantation.

It is indeed time for Australia to reflect on the kind of society it wishes to become (p.24). Australia now has the opportunity to set an example for the rest of the world.

CRT strongly urges the NHMRC to enact a moratorium on human clinical xenotransplantation trials, ban all animal-based xenotransplantation research now, and place a hold on the development of these guidelines until it has conducted extensive public consultations.

Sincerely,

Alix Fano, MA
Director
On behalf of CRT's 3 million members

¹ Some of these issues are addressed for the U.S. in Fano A., et al. *Of Pigs, Primates and Plagues: A Layperson's Guide to the Problems with Animal-to-Human Organ Transplants*. Medical Research Modernization Committee, New York, 1997 (enclosed).

² We found numerous biased statements in the guideline, such as: "[A] moratorium on such clinical [xenotransplant] research is not appropriate," (p.xix); Xenotransplantation is described as an "innovative approach," (p.5); "If the technical issues can be overcome, pig pancreatic islet cell xenotransplantation has the potential for widespread clinical application," (p.54);

³ "We believe that with centralized oversight and really strict framework and guidelines that we can . . . over the next few years put our toe in the water safely," Dr. Breen told a media briefing." Judy Skatssoon. Bid for pig-to-human transplant trials despite virus fear. *The Canberra Times* online. 8 August 2002 "The council's xenotransplantation working party, chaired by ethicist Kerry Breen, has tentatively approved the practice and is in favor of allowing clinical research to take place." AAP. Forum to discuss ethics of animal transplants. *The Canberra Times* online. 12 August 2002.

⁴ The working party has concluded that "inherent ethical objections [described in Chapter 3] can be satisfactorily answered," (p.11). Mohacsi, Thompson, and Quine state that "some researchers and clinicians have chosen to ignore negative attitudes towards clinical xenotransplantation, assuming that people will automatically embrace this new technology when it becomes available. [But a] review of eight studies . . . did not find overwhelming support for it." Mohacsi PJ, Thompson JF, Quine S. Attitudes to xenotransplantation: scientific enthusiasm, assumptions and evidence. *Ann Transplant* 1998; 3 (2): 38-45.

⁵ Anon. Canadians not ready for animal-to-human transplants. *Canadian Medical Association Journal* online, January 8, 2002. Source: www.cma.ca/cmaj//cmaj_today/2002/01_08.htm.

⁶ In the U.S. chronic diseases account for more than 60% of the nation's medical care costs. Source: Centers for Disease Control. About Chronic Disease. www.cdc.gov/nccdphp/about.htm.

⁷ Binns CW, Leong JF. Public health nutrition: results and research. *Asia Pac J Public Health* 2000; 12 Suppl: S18-20.

⁸ Ornish D, et al., Intensive lifestyle changes for reversal of coronary heart disease. *JAMA* 1998 Dec 16; 280 (23): 2001-7.

⁹ Plans-Rubio P. Cost-effectiveness of cardiovascular prevention programs in Spain. *Int J Technol Assess Health Care* 1998 Spring; 14 (2): 320-30. Brunner E, Cohen D, Toon L. Cost-effectiveness of cardiovascular disease prevention strategies: a perspective on EU food based dietary guidelines. *Public Health Nutr* 2001 Apr; 4 (2B): 711-5.

¹⁰ According to the U.S. Centers for Disease Control, smoking cessation interventions, which cost \$2,587 for each year of life saved, are the most cost-effective of all clinical preventive services. Source: www.cdc.gov/nccdphp/about.htm.

¹¹ Felber JP, Golay A. Pathways from obesity to diabetes. *Int J Obes Relat Metab Disord* 2002 Sept; 26 Suppl 2: S39-45.

¹² Van Dam RM, et al. Dietary Patterns and Risk for Type 2 Diabetes Mellitus in U.S. Men. *Annals of Internal Medicine*. 5 February 2002; 136(3): 201-9.

¹³ American Diabetes Association. The prevention or delay of Type 2 diabetes. *Diabetes Care* 25: 742-49, 2002.

¹⁴ Source: www.cdc.gov/nccdphp/about.htm.

¹⁵ National Public Health Partnership, (Victoria) Department of Human Services. Preventing chronic disease: A strategic framework. Background paper. October 2001. Source: www.dhs.vic.gov.au/nphp/chrondis.

¹⁶ The Center for Human Islet Transplantation in Seattle comprises 7 institutions in the Northwestern U.S. The Center grows human islets in culture, while the Puget Sound Blood Center serves as an islet bank, isolating and storing islets for transplant

programs on the West Coast. See www.isletservice.org/centers/seattle.htm. See also Miyamoto M. Current progress and perspectives in cell therapy for diabetes mellitus. *Hum Cell* 2001 Dec; 14(4): 293-300, which discusses growing human pancreatic beta islet cells in vitro. Researchers at the University of Alberta in Edmonton, Canada have developed the Edmonton protocol using human islet cells to treat type 1 diabetes. They have reversed insulin dependence in seven patients for over one year. Anon. Joslin Part of Ten Site, Worldwide Clinical Trial of Islet Transplants Using Edmonton Protocol. Source: www.joslin.harvard.edu/news/islet_transplant_july.shtml.

¹⁷ Hoekstra R, Chanuleau RA. Recent developments on human cell lines for the bioartificial liver. *Int J Artif Organs* 2002 Mar; 25 (3): 182-91.

¹⁸ Richards M, et al. Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cells. *Nature Biotechnology* 5 August 2002 online.

¹⁹ Tintner R, Jankovic J. Treatment options for Parkinson's disease. *Curr Opin Neurol* 2002 Aug; 15 (4): 467-76. The authors state that "implantation of fetal . . . tissue and other grafts . . . is associated with significant complications and remains experimental." Van Der Laan LJW et al. (2000) Infection by porcine endogenous retrovirus after islet xenotransplantation in SCID mice. *Nature* 7 September 2000; 407:501-504. The authors suggested that pig islet xenotransplantation to humans may result in long-term exposure to replication-competent endogenous retrovirus.

²⁰ Gallup Poll conducted for the Partnership for Organ Donation, March 1993.

²¹ A U.S. General Accounting Office report on organ donation (April 1998) suggested that the number of available organs in the U.S. may be much higher than previously thought. General Accounting Office. Organ Donation: Assessing Performance of Organ Procurement Organizations. (GAO, Washington, DC, April 8, 1998). Evans RW, Orians CE, Ascher NL. The potential supply of organ donors. An assessment of the efficacy of organ procurement efforts in the United States. *JAMA* 1992 Jan 8; 267 (2): 239-46.

²² This seems to have increased organ donation rates in South Australia from 15 per million in 1995 to 23 per million in 1998.

²³ Pearson IY, Chapman JR. Improving organ donation rates. *MJA* 17 May 1999; 17 (10): 463-4.

²⁴ Hibberd et al have suggested that the donor rate in NSW could be increased 70-80% by overcoming the reluctance of medical practitioners to resuscitate missed potential donors and by gaining permission for organ retrieval from next of kin. Hibberd AD, et al. Potential for cadaveric organ retrieval in New South Wales. *BMJ* 1992 May 23; 304 (6838): 1339-43.

²⁵ It does not appear from this guideline (p.16) that Australians have adequately considered the option of "presumed consent" legislation. If enacted, such a law could potentially solve the organ shortage. Fisher J. An expedient and ethical alternative to xenotransplantation. *Med Health Care Philos* 1999; 2 (1): 31-9. Gnant MFX. The Impact of the Presumed Consent Law . . . : Quadruplication in the Number of Organ Donors. *Transplantation Proceedings*, Vol. 23, No. 5 (October 1991): 2685-6. Roels L et al. Effect of a Presumed Consent Law on Organ Retrieval in Belgium. *Transplantation Proceedings*, Vol. 22, (1990): 2078-9.

²⁶ Gullifer J, Gill J. Organ Procurement for Transplantation: Options for Increasing Organ Availability in Australia. Proceedings of the Inaugural Clinical Research Conference in Anthony O'Brien, ed. *Proceeding of the Inaugural Nursing Research Conference: Research for the Future. Universities and Health Services in Partnership*. Armidale NSW, The Mid Nth Coast Health Service & University of New England, Armidale NSW, 130-39, 1997.

²⁷ One American study found that families of potential organ donors are receiving inadequate information to make informed choices about organ donation, and their emotional needs are not always met. Beaulieu D. Organ Donation . . . *J. Neurosci Nurs* 1999 February; 31(1): 37-42. Another found that, the investment of race-sensitive personnel in large urban county trauma facilities can result in a significant increase in donor conversion rates. Shafer T et al. An in-house coordinator program to increase organ donation in public trauma hospitals. *J Transpl. Coord* 1998 June; 8 (2): 82-7.

²⁸ W. DeLong. Options for Increasing Organ Donation: the Potential Role of Financial Incentives, Standardized Hospital Procedures, and Public Education to Promote Family Discussion. *Milbank Q* 1995; 73 (3): 463-79.

²⁹ Vigneau C, et al. Is there an age limit for organ donors? *Ann Fr Anesth Reanim* 2001 Oct; 20 (8): 723-6. Gridelli B, Perico N, Remuzzi G. Strategies for a greater supply of organs for transplantation. *Recenti Prog Med* 2001 Jan; 92 (1): 9-15. The

following study found that kidneys and livers can be transplanted from older donors with positive outcomes. Coleman-Musser L et al. Discard Rates and Transplant Outcomes in Organs Recovered From Older Donors. *J. Transpl. Coord* December 1997; 7 (4): 190-4. Jordan ML et al. High-Risk Donors: Expanding Donor Criteria. *Transplantation Proceedings* 1999; 31: 1401-3.

³⁰ Lewis DD, Valerius W. Organs from Non-Heart Beating Donors: An Answer to the Organ Shortage. *Critical Care Nurse* April 1999; 19 (2): 70-4.

³¹ Hughes J. Xenografting: Ethical Issues. *Journal of Medical Ethics* 1998; 24: 23-4.

³² Krauz I. Donated liver split for two patients. *The Ha-aretz*, Israel, April 22, 1999.

³³ Danninger F, Breza J, Mraz P, Petrasovic M. Procedure for multiorgan procurement (heart, liver, kidneys). *Bratisl Lek Listy* 1995 Dec; 96 (12): 651-4.

³⁴ Anon. Surgery Staves Off Heart Transplant. Reuters, March 17, 1997.

³⁵ *New York Times* science reporter Sheryl Gay Stolberg, who visited a transgenic pig breeding facility, described the sight of a pregnant female pig, upside down on an operating table, her head suspended over a bucket to catch vomit, “her insides splayed out on a blue-paper surgical drape as a scientist rearranges the DNA of her unborn young.” The mother pig’s eggs are flushed out of her ovaries, human genes are inserted into each egg, and the manipulated embryos are implanted back inside her. Perhaps one out of 20 piglets will be born with human genes. The rest are killed. Stolberg SG. Could This Pig Save Your Life? *The New York Times Magazine*, October 3, 1999, pp.47, 49.

³⁶ Langley G, D’Silva J. Animal Organs in Humans” Uncalculated Risks & Unanswered Questions. Compassion in World Farming UK/British Union for the Abolition of Vivisection, October 1998.

³⁷ Coghlan A. Hidden Sacrifice. *New Scientist*, May 8, 1999.

³⁸ Browne A. When Science Makes a Pig’s Ear of it. *New Statesman* (UK), 15 November 1999.

³⁹ Groth CG, et al.. Transplantation of Porcine Fetal Pancreas to Diabetic Patients. *The Lancet* 19 November 1994; 344: 1402.

⁴⁰ In 1999, in a Diacrin-sponsored trial to treat Parkinson’s Disease, 18 patients each had 48 million fetal pig cells transplanted into their brains. Source: www.diacrin.com/prod01.htm.

⁴¹ The HepatAssist device, used to support patients with acute liver failure, uses 5 billion pig liver cells in each treatment. The average is three to four treatments per patient. Zorina Pitkin of Circe Biomedical quoted in minutes of an FDA Xenotransplant Subcommittee meeting, June 3, 1999, Washington, DC, Source: <http://www.fda.gov/ohrms/dockets/ac/99/transcript/3517t1.rtf>.

⁴² Holden P, McGlone J. Animal Welfare Issues: Swine. *AWIC Bulletin* Spring 1999; 9 (3-4): 9-11. Undercover video of transgenic pigs raised for xenotransplantation research obtained by the BUAV in July 1999 clearly demonstrated this behavior.

⁴³ Jones J. Cloning May Cause Health Defects. *British Medical Journal* 8 May 1999; 318: 1230. Fox MW. Beyond Evolution: The Genetically Altered Future of Plants, Animals, the Earth, and Humans (The Lyons Press, 1999), pp.107-15.

⁴⁴ Anon. Cloned animals have high risk for fatality. *DVM* the newsmagazine of veterinary medicine, online, August 20, 2002. Source: www.dvmnewsmagazine.com/dvm/article/articleDetail.jsp?id=28963.

⁴⁵ See PubMed online and type in the word “xenotransplantation.”

⁴⁶ See Draft UK Xenotransplantation Report and highlighted sections in the Food and Drug Administration, Biological Response Modifiers Advisory Committee, Xenotransplant Subcommittee, meeting minutes, June 4, 1999.

⁴⁷ See pages 39, 40, 41, 42, 45, 48, 49, 50, 53, 58 in the Food and Drug Administration, Biological Response Modifiers Advisory Committee, Xenotransplant Subcommittee, meeting minutes, June 4, 1999.

⁴⁸ The leaked documents were also analyzed by the Royal Society for the Protection of Cruelty to Animals (RSPCA) and the results published in the report, *RSPCA Report: Non-Human Primates in Xenotransplantation Research in the UK* (21 June 2002), (see enclosed).

⁴⁹ www.novartis.com, as of August 31, 2002. Clearly, Novartis did not lack the resources to monitor its xenotransplantation research.

⁵⁰ This guideline (Section 3 and elsewhere) assumes that it is acceptable to raise and kill animals for food (and, by logic, for xenotransplantation). But As Hughes states, “we are not all agreed on the acceptability of eating meat.” Hughes J. Xenografting: Ethical Issues. *Journal of Medical Ethics* 1998; 24: 18-24. Indeed, society is not of one mind on the

acceptability of pig slaughter as attested to by the growing number of vegetarians and the success of movies like 'Babe' – a story about a pig who learns to be useful on a farm to avoid the slaughterhouse. According to Reuters Australia, "Such has been audience identification with the film's plucky porcine hero that the pork industry has complained about a fall in sales." Reuters Canberra. And this little piggy went to the Oscars. February 15, 1996. Source: www.canoe.ca/JamMoviesArtistsN/noonan_chris.html.

⁵¹ Here is an account from a worker assigned to unloading pigs: "In the winter, some hogs come in all froze to the sides of the trucks. They tie a chain around them and jerk them off the walls of the truck, leave a chunk of hide and flesh behind. They might have a little bit of life left in them, but workers just throw them on the piles of dead ones. They'll die sooner or later." Once at the slaughterhouse, some animals are too injured to walk and others simply refuse to go quietly to their deaths. This is how the workers deal with it: "The preferred method of handling a cripple is to beat him to death with a lead pipe before he gets into the chute... If you get a hog in a chute that's had the shit prodded out of him, and has a heart attack or refuses to move, you take a meat hook and hook it into his bunghole (anus)...and a lot of times the meat hook rips out of the bunghole. I've seen thighs completely ripped open. I've also seen intestines come out."

⁵² Editorial. The Curse of Factory Farms. *The New York Times* August 30, 2002.

⁵³ See Fano A 1997 for references and discussion.

⁵⁴ Chari RS, et al. Brief Report: Treatment of Hepatic Failure with Ex Vivo pig-liver perfusion followed by liver transplantation. *NEJM* July 28 1994; 331 (4): 234-7.

⁵⁵ http://www.mayo.edu/news/Mayo_ROCHESTER/transplant/backgrounder.html.

⁵⁶ Washburn J. Informed Consent. *Washington Post Magazine*. December 30 2001, pp.8-13, 23-26.

⁵⁷ In January 2000, CRT filed a motion asking a Federal Court to order the U.S. Food and Drug Administration (FDA) to disclose almost 40,000 pages of agency documents on side-effects and deaths in clinical xenotransplant trials. Some 470 patients have been treated with xenotransplant products since 1992 - many before the issuance of any guidelines. CRT's brief reveals that by December 1997, one xeno trial sponsor, Diacrin, had already documented 232 adverse events in connection with clinical testing of its NeuroCell-PD product alone, which uses pig cells to treat Parkinson's Disease. The precise number of adverse events in xenotransplant trials is unknown because FDA keeps that information secret. Since 1992, at least 16 patients have died during or after xenotransplant trials. Eight patients died in 1997 after having their blood "filtered" through pig livers at Cedars Sinai Medical Center in Los Angeles. A year later, another patient died at the Mayo Clinic in Rochester, Minnesota after undergoing a similar procedure.

⁵⁸ Ronchi E. Biotechnology Unit, Organisation for Economic Cooperation and Development, *Advances in Transplantation Biotechnology and Animal to Human Organ Transplants (Xenotransplantation)*. OECD, Paris, 1996, p.78. This report states that the development of xenotransplantation "may conflict with efforts to keep medical costs down; may contribute to the development of multi-tier medicine; may conflict with efforts to develop better approaches to preventive medicine; may discourage donation of [human] organs for allotransplantation; [and] may not be consistent with striving for humane and fair medicine."

⁵⁹ See enclosed report *Animal Organs in Humans* (Langley & D'Silva, 1998) for references regarding the anatomical, physiological, and biochemical differences between pigs and humans.

⁶⁰ Daar AS. Animal-to-Human Organ Transplants – a Solution or a New Problem? *Bulletin of the World Health Organization* 1999; 77 (1): 55.

⁶¹ Transcript of the Food and Drug Administration's, Biological Response Modifiers Advisory Committee, Xenotransplant Subcommittee meeting, June 4, 1999. Draft UK Xenotransplantation Report, Dan Lyons, Uncaged, 2000.

⁶² Although pig cells are being transplanted into various animal species (rat, monkey, etc.) to "treat" neurological diseases like Parkinson's and Huntington's diseases, animals do not get these diseases. They are uniquely human. In order to produce *symptoms* of these diseases in animals, the animals typically must have parts of their brains surgically damaged or destroyed. This does not mimic the human clinical situation physiologically, therefore the results of such studies must be questioned.

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- ⁸¹ Tacke SJ, Kurth R, and Denner J. Porcine endogenous retroviruses inhibit human immune cell function: risk for xenotransplantation? *Virology* 2000 Mar 1; 268 (1): 87-93.
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- ⁹⁹ World Health Organization. *World Health Report 1996, Executive Summary*. WHO, Geneva, Switzerland, p.4.
- ¹⁰⁰ The U.S. Public Health Service published guidelines and established a national xenotransplantation committee in 2001 after several dozen clinical trials involving almost 500 patients had already been conducted. Current guidelines are voluntary and non-binding; patients cannot be forced to comply with monitoring procedures and may drop out of trials at any time. No xenotransplant patient registry currently exists. Are current patients faithfully reporting all of their close contacts to the FDA? Have those people, if they have been identified, agreed to register themselves with authorities and submit to blood tests and the like? One xenotransplant patient went on television some years ago and acknowledged that he had fathered a child. That would be “discouraged” today under the current set of guidelines, for fear of germline transfer of pig viruses to offspring. Will regulators force patients not to have children? Unlikely. And we must assume, because we do not know, that patient and animal tissue samples are in the possession of biotech companies, which may not be the best place for them. We still do not know what all of this is costing U.S. taxpayers, and we do not know what steps have been put in place to deal with any potential disease outbreaks resulting from a novel pig virus.
- ¹⁰¹ In its 1995 report, *HIV and the Blood Supply*, the U.S. Institute of Medicine revealed “several weaknesses in the FDA’s regulatory approach to blood safety issues,” IOM stated that “[m]any blood bank officials during this period publicly denied that AIDS posed any significant risk to blood recipients,” and when confronted with new information about disease risks, the FDA failed to change its blood safety policies despite opportunities to do so. The report cited a “failure of leadership” which led to “less than effective donor screening, weak regulatory actions, and insufficient communication to patients about the risks of AIDS,” as well as decisionmaking compromised by “personal or institutional biases.”
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¹⁰⁴ Associated Press. Hospital infection deaths in focus. July 21, 2002.

¹⁰⁵ Vincent CA. The human element of adverse events. *Medical Journal of Australia* 1999; 170: 404-5.

¹⁰⁶ Abbey Meyers, public representative, speaking at the Food and Drug Administration's, Biological Response Modifiers Advisory Committee, Xenotransplant Subcommittee meeting, June 3, 1999. Transcript.

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¹⁰⁸ Adapted from the Wingspread Statement on the Precautionary Principle, source: <http://www.monitor.net/rachel/r586.html>.

¹⁰⁹ "Several breakthroughs have already been achieved . . . that make success seem more likely," (p.3), and

"[R]outine clinical practice is not likely to occur in the foreseeable future." (p.20).

"[T]he anatomy and physiology of pigs are similar to those of humans," (p.xxxviii) and

"The major obstacles to successful xenotransplantation include anatomy and physiology." (p. xxxix).

"The goal is to obtain good information about what can be expected to happen in a human situation (eg by using nonhuman primates as organ recipients)," (p.18) and "[E]stimates of efficacy in baboons may not reflect what is achievable in humans," (p.59), and "[S]tudies with nonhuman primates . . . do not fully determine the equivalent response in humans," (p.60).