Pennington's Sweetie Pie

Robert Pennington was a normal healthy seventeen-year-old working in a family-owned carpet store when he came down with what he thought was the flu. After a few weeks, he was not feeling better, and in fact, he felt much sicker. A glance in a bathroom mirror revealed that the whites of his eyes had turned yellow.

Alarmed, Robert went to a local medical clinic where the physician saw him. The doctor examined Robert and asked for a urine sample. Astounded by the coffee-colored brown urine sample, the doctor referred Robert to a specialist. Four days later, Robert was admitted to Baylor University Medical Center diagnosed with sudden and overwhelming liver failure.

Dr. Marlon Levy, a transplant surgeon at Baylor, knew that Robert would die in a few days without a liver transplant and reacted immediately by placing Robert at the top of the transplant list. However time was critical since Robert was showing signs of acute ammonia poisoning as a result of the liver's inability to clean toxins from his blood. He was already hallucinating and approaching a comatose state. Dr. Levy soon realized that no human liver would be available in time to save Robert's life.

Dr. Levy began to evaluate another possibility. An experimental procedure known as extracorporeal perfusion using a transgenic pig liver had been approved by the FDA for testing at Baylor Medical Center. This research was funded by a company that had developed a process to insert human genes into pig liver cells to prevent humans from rejecting a transplanted pig liver. The company then sought research hospitals willing to test the transgenic pig livers on humans with liver failure who needed a new organ. The data collected and the outcomes of these experimental surgeries, if positive, would be submitted to the FDA to support a marketing application.

The company had shipped the transgenic animals to the Baylor animal labs and they were there at the time that Robert Pennington was admitted to the hospital. Dr. Levy had also been trained in the use of these pig livers in extracorporeal perfusion. This procedure involves removing the patient's blood through plastic tubing and cleansing it by passing it through the pig liver before returning the blood to the patient. This is a temporary measure referred to as a "bridge to transplant", and it is intended to support liver function and the patient's life until a suitable human liver can be found.

Within a short time, Robert lapsed into coma and was placed on life support. Dr. Levy notified Robert's grandmother, his guardian, that she was needed in the intensive care unit for a discussion on Robert's condition. Charlotte Pennington listened as Dr. Levy explained the procedure. He also explained that, since the procedure was new, there were unknown risks that included the possibility that some dangerous animal viruses might infect Robert. He would need to be tested for animal source infections possibly for the rest of his life. Dr. Levy also told Mrs. Pennington that Robert would be his first pig liver transplant patient. Mrs. Pennington gave her consent the next morning.

Dr. Levy then removed the liver from a 15-week-old, 118-pound transgenic pig from the Baylor animal lab and moved it to Robert's bedside to be used as Robert's external support liver. Shortly after the liver was attached to Robert through the plastic tubing, perfusion began and was used for six and half hours over three days. At that point, a suitable human liver for Robert was found in Houston and delivered to Baylor for transplant. The transplant was successful and Robert made a full recovery. However, no one could forget that his survival was due to the experimental procedure Dr. Levy used to keep Robert alive until the human liver was found. In fact, Robert's grandmother keeps a snapshot of the pig, named Sweetie Pie by one of Baylor's animal handlers, in a scrapbook.

Sailing into uncharted waters, Pennington (with his grandmother) was the first subject of an experimental procedure in which his blood was circulated through a pig's liver outside his body. While all went well with Robert Pennington (and another 5 patients who received the same experimental surgery), the FDA shut down the perfusion trial three weeks after Robert's procedure. A group of virologists in England had found evidence that human cells could be infected with pig viruses* in test tubes and that the genes for two separate viral strains had been found in several varieties of pigs, making it unlikely that pigs could be bred to remove the virus.

No one knew at the time whether pig viruses could make humans sick but precaution seemed justified. Ultimately, the FDA lifted the ban when companies producing transgenic pigs developed a pig viruses detection test for both pigs and patients. Yet, this test alone did not resolve concerns about the infectious risk. The fact that pig viruses had been undetectable with any test for many years led researchers to suspect that pig tissues could harbor other unknown infectious agents.

**porcine endogenous retroviruses*

This case is derived from: Stolberg, S.G., Could this pig save your life? New York Times, October 3, 1999.

Classroom Teaching Example

This section describes how the Pennington Case might be used in a classroom incorporating elements of the Lesson Strategies included in this Ethics Primer.

This example focuses particularly on the use of a Decision-Making Framework, as well as a Case Study approach.

Decision-Making Framework Elements

1. Ethical Question: Identify the ethical problems confronted by the actors in the case. What has to be decided?
   - Should animals be used in research to provide "bridge organs"?
   - How do we treat patients ethically in end stage of their disease?
   - How should we balance the potential benefits of genetic engineering with the possible risks to public safety?
2. Relevant Facts: Assess the factual information available to the decision makers.
   - How are the animals cared for in lab facilities or any research facilities?
   - Who monitors research facilities that house animals?
   - What is the therapeutic worth of using pig livers as bridge transplants as opposed to mechanical devices? When should the use of a bridge organ be proposed for a patient (i.e., at what stage of their disease)?
3. Stakeholders and Values: Identify the "stakeholders" in the decisions and their concerns/values.

   Who has a stake in this decision?
   - Patients and families
   - Doctors, researchers, and the surgical team
   - Animal caretakers
   - Donor animals
   - Insurance companies
   - Biotech companies
   - FDA
   - Patients that may benefit from further animal research

In what ways might each stakeholder be affected?

- Human patients must consider their life, health and the well being of their families (financial and emotional burdens)
- Families and friends of the patients will be invested in the well being of the patient.
- Doctors, researchers and surgical teams will be affected by knowledge gained, prestige of success and their own satisfaction in providing patients with life saving measures.
- Animal caretakers may or may not be distressed by the use of the animals in this research study.
- The lives and well being of animals raised to human purpose should be considered.
- The health care system and society in general may be asked to share a financial burden.
- Society in general may be put at risk for undetected viruses or other infectious agents.
- The research company has business interests in the success of the therapy.
- Stockholders in the research company stand to gain with successful therapies; stand to lose with catastrophic therapies.
- Regulators must develop guidelines to govern the research and implementation of these therapies.
- Transgenic organs will reduce the waiting time for patients in organ failure.

Identify the values at stake in the decision

- Promotion of human and animal well being
- Protection from risk – the avoidance of harm or injury to others (non-maleficence)
- Compassion – sympathetic and caring response to others
- Fairness – a procedure for decision making that respects the concerns of all involved
- Justice – the distribution of harms and benefits
- Risk perception – assessing the likelihood and severity of potential harms
- Pursuit of scientific inquiry (integrity in scientific inquiry)
- Relief of animal and human suffering from disease through research development
- Protection of the innocent
- Economic profits

4. Possible Solutions: Identify the options available to the decision makers
    - With FDA approval, research with "bridge transplants" could be allowed in limited circumstances to provide patients in end-stage disease a chance of survival until a suitable human organ is found. This would also provide the researchers with more data.
    - Continue other research with transgenic animals that may have therapeutic benefits in Parkinson's and diabetes, but discontinue use of transgenic animals as "bridge transplants".
    - Perfect mechanical liver perfusion for patients in end-stage disease.
    - Place patients on transplant waiting lists in the hope of receiving a suitable organ. Advocate for social change in increasing the number of available donor organs through educational programs.

Case Study Approach

Have students form groups based on the 4-6 stakeholder groups identified as most important to this case. For example, students could be grouped into researchers, doctors, veterinarians, animal activists, patients and families, insurance companies, etc.

Have each group derive the concerns and values that are most important to them. If time permits, have each group conduct research on their stakeholder. If time is limited, provide each group with a 'position sheet.'

Create mixed groups consisting of students from each individual group. Have students present the position of their stakeholder to the mixed group. Allow the groups time to come to consensus on an ethical issue related to the case, or ask them to clarify the nature of their disagreement.

Afterwards, allow individual students to present their own position through a debrief session or through a written assignment.

Extension Activities:

Anatomy and Physiology:

Have students research the anatomy and physiology of the liver. This should include the normal development, structure, and function of the liver. Review the tests used to determine normal liver function and disease state. Encourage students to consider the quality of life issues surrounding someone in organ failure. Have the students link the symptoms of Robert Pennington to the physiology that they have learned.

Transplant Information:

Have students access the United Organ Sharing Network for information on:

- The number of people currently waiting for transplants
- The number of transplants that occur annually and the organ type
- The number of medical centers performing transplant surgery
- The cost of a liver transplant and the necessary follow up care
- The tissue match criteria for a successful liver transplant
- The types of tissue and solid organ transplants

Ethical Analysis of the Case: Pennington's Sweetie Pie

Robert Pennington's case exemplifies both the promise and potential peril associated with the introduction of genetically modified therapeutic animal tissues into humans. The creation of bioengineered animals as a source of tissue to treat human disease is a rapidly progressing phenomenon that has raised several practical, scientific, medical, regulatory, ethical, and social policy concerns.

Practical problems include the access to an appropriate source and number of suitable animals. Scientific concerns include the ability to adequately and reproducibly "humanize" animals with genetic alterations that effectively prevent tissue rejections in human recipients. Medical problems include the potential that these animals are a source of undetectable zoonotic infections that can infect the human recipients with symptoms arising sometimes years after transplantation during which time the patient may pass the infection to others. Other medical problems include the unknown longevity of animal organs, the degree to which they can eliminate severe organ failure, and the inability to predict the risks (both immediate and long term) of the transplant procedure. Since the field of xenotransplantation is advancing at such a fast rate, regulatory systems such as the FDA often lag behind the technology development, resulting in inconsistent and spotty controls and guidelines. Also, since corporate scientists many times hold the expertise in the field, FDA learning often comes from the companies the FDA is authorized to regulate. The combination of the promise of the technology and the related concerns (1) has generated multiple ethical and social policy issues and concerns that this teaching module is designed to address.

The ethical and social issues linked to xenotransplantation to date include:

Use of Animals

The protest of animal rights activists is exemplified by the statement of one such group: "Should xenotransplantation ever become a reality, pigs will be turned into spare part factories, plundered for their organs. Genetically-mutated and raised in artificial conditions, these remarkably intelligent animals face an unnatural and distressing existence." (2) The questions that flow from a concern about animal welfare include:

- What acuity of human need justifies the use of animals to obtain therapeutic tissue and organs?
- Are the numbers of animals used in the process of developing the technology justified?
- Is the process of retrieving tissues and organs humane?
- How do we balance the need to save human lives and improve human health with the need to respect the lives of animals?

Human research integrity

In order to justify the introduction of xenotransplantation into humans, research must be able to demonstrate that the benefits to the patient of the experimental treatment outweigh the risks. This is a difficult task, many argue, since too much is unknown about the consequences of xenotransplantation. Yet, others argue that lab and animal research are never sufficient to be able to predict human risks and benefits with any degree of reasonable surety.

A second important consideration relates to the integrity of human subject consent.

Since the patients on an organ transplant waiting list are often close to death and therefore desperate, can they rationally weigh and balance the information about the consequences of animal organ transplantation to provide free and full and valid consent? How do researchers responsibly balance the need for informed consent, take into account the vulnerability of the potential human subjects, and still pursue this potentially valuable research.

Timing of deployment

The great medical need for organs and the absence of viable therapeutic alternatives drives this technology development. The fact that patients with failing organs will often die before a suitable human organ is available tempts physicians to deploy the technology to save a life despite the lack of full understanding about the consequences of the transplant. Some ethicists believe that patient need and the lack of other options makes it ethically defensible to proceed with research despite the unknowns(3). The drive to introduce transgenic xenotransplantation in humans has been lauded by some who view these physicians as heroes willing to take risks on behalf of the preservation of human life. Others criticize scientists and doctors who push the envelope and suspect that their pursuit of personal glory drives them more than does a concern for patient welfare. These differing views often influence the speed with which new medical technologies are deployed in humans. And when they are deployed, there is always a question about whether more research is needed to ensure patient benefit. This question was addressed by one ethicist who wrote that "There is a widespread misperception that medical treatments and surgical procedures are easily classified as either experimental or accepted. In fact, all treatments have an element of experimentation, and new surgical procedures are based on extrapolations from prior work...When does a surgeon decide to apply a new operation to a patient?...the decision is based on balancing, on the one hand, the experimental evidence suggesting that the procedure may succeed, and, on the other, the clinical urgency..." (4)

Regulatory integrity

Commensurate with the ethical concerns above, commentators have asked whether the FDA has prematurely approved the use of bioengineered livers. Faith in the regulatory system can falter when, as in the case of xenotransplantation, the Agency approves of and then halts research because of the risk of harm to human subjects. In light of this public trust issue, others have asked whether the regulatory agencies should consider public as well as scientific opinion before approving human research on xenotransplantation. A European poll at the time showed that only 36% of people found xenotransplantation acceptable. In another poll, those in Britain were only 21% in favor. Others take a different approach and favor proceeding with the research but only under careful controls. The problem with this approach is that consensus on the definitions of transplant success and what constitutes adequate control and surveillance is not widespread and is likely to change as information advances.

Patient welfare

Concern for patient welfare prompts several questions:

- How many liver failure patients can be sacrificed in the process of researching the efficacy and safety of animal tissue transplantation in humans?
- How much should be known about the risks (including that of zoonoses) before the deployment of bioengineered pig tissues into humans with organ failure?
- What constitutes a reasonable balance of risks and benefits from animal organ transplantation?

Obviously, differences of opinion exist with respect to each of these questions.

Some argue that any survival benefit is justified in patients facing imminent death and any delay in the research will only lead to more deaths from organ failure.

Critics argue that we should not proceed in the face of unknown and potentially dangerous adverse consequences since we are "literally, interfering with something we do not understand." (5)

Public safety

Retroviruses such as PERV (Porcine Endogenous Retroviruses) and HIV (Human Immunodeficiency Virus) integrate into the DNA of the cells that they infect, allowing them to persist in the infected individual or animal indefinitely. Also, animals can pass infectious agents to humans, such as the prion that causes Bovine Spongiform Encephalopathy (BSE or "mad cow disease") in cattle and variant CJD in humans. The prospect of confronting infectious agents like these in xenotransplant patients (zoonotic infection) who might infect others worries some scientists, public health officials, and regulators.

As one alarmed researcher put it, "The individual can sign a consent form and say, 'I'll take the risk because I'm going to die anyway.' But that person is signing a consent form for the whole population, the whole human race." (6) To prevent such contamination, the United Kingdom agency charged with producing guidelines for xenotransplantation advised that recipients of animal organs be required to sign a document of consent agreeing to be perpetually monitored for signs of infection, to take drugs for the rest of their lives to maintain their health, to use barrier contraception constantly, to have their sexual partners consistently monitored, and to refrain from pregnancy or fathering a child.

Commercialization conflicts of interest

Any time that companies sponsor research on products intended for a lucrative market, conflicts of interest concerns arise. This is especially the case when a small biotechnology company is relying on its first product to sustain corporate viability. This situation prompts questions about whether the promise of profits prompts companies to engineer the clinical trial protocols to enhance the probability of good outcomes or to push the technology into human trials prematurely. The concern about conflicts is heightened in situations where the regulatory agencies must rely on corporate scientists to become sufficiently informed about the technology to promulgate regulatory guidelines.

Distributive justice and the cost of medical care

In 1996, the Institute of Medicine calculated that if animal organs made it possible to offer a transplant to everyone in the United States who needed one, annual medical treatment expenditures would rise to $20.3 billion, from $2.9 billion.(7) This cost estimate prompts the question of whether the potential benefit to organ failure patients is sufficient to justify the risk that constraints on medical budgets will lead to denial of medical care to patients with other diseases.

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Ethical Concerns Regarding Genetic Modification of Organisms

The genetic modification of plants and non-human animals normally involves the alteration of individual traits to increase the usefulness of the organism for human purposes. Genetically modified (GM) crops may be more productive, more resilient, or more resistant to insects or disease than their natural, non-modified counterparts. Similarly, animals may have GM traits that make them more efficient sources of food or other useable products. Proposed genetic modifications in human beings involve either the alleviation of disease or disability caused by some genetic malfunction or abnormality of the individual or the attempt to enhance the phenotypic properties or functioning of the individual.

Although the genetic modification of plants and animals tends to be widely accepted in North America and Asia, it has been more controversial in Europe and in some developing countries, particularly in Africa. There are basically three sources of ethical controversy in the area of GM plants and animals.

First, some believe that ethical principles of justice, respect, dignity, the avoidance of suffering, and rights all apply to at least some species or forms of life other than human beings. According to this perspective, plants and animals should not be used instrumentally as a means to an end, but should be respected as an object of integrity in their own right. Proponents of this view argue that inherited genetic structures of individual plants and animals, or whole species, should not be deliberately altered without good reason.

The second basis of ethical concern on the topic of GM plants and animals is the potential risk to natural evolution, ecosystems, and to human health and well-being. Some feel that in the field of genetics, human scientific and technical knowledge may exceed human wisdom and prudence. Critics would say that while GM has the potential for tremendous human economic and health benefits, it has the potential for catastrophic mistakes and dangers as well.

For instance, genetic modification in agriculture tends toward genetic simplification of a population or species and undermines genetic and biological diversity. Over long periods of time, species that are genetically diverse have a greater capacity to adapt and survive in the face of changing evolutionary and environmental pressures. Genetic modification practices increase the need for human, technological support to ensure the survival of genetically simplified species, hence the increased use of insecticides and fertilizers. Over time, genetic modification may contribute to the decline of biodiversity and the disappearance (extinction) of species that is now occurring worldwide at an alarming rate. Moreover, genetically modified organisms that come into uncontrolled contact with natural organisms may spread the modified traits across an entire habitat. Genetically modified corn that was intended for use only in animal feed, for example, became accidentally mixed with corn intended for human consumption. The discovery of this

accident caused considerable economic disruption because the GM species was associated with serious allergic reactions and other health risks in some persons.

The third source of ethical controversy surrounding genetic modification in plants and animals derives not so much from the biological aspects of GM itself as from its social, economic, cultural and political implications. In areas where it has been widely developed, GM in agriculture has tended to alter patterns of family farming and landholding, giving competitive advantage of larger types of agro-business and making farmers more dependent upon the international corporations that own seed-lines and sell the kinds of pesticides and fertilizers that GM crops require. In the developing countries, genetic technologies have prompted countries to emphasize monocultural practices and to abandon crop rotation in favor of intensive fertilizer use. This has often made developing economies and the agricultural labor force in developing countries vulnerable to shifts in global commodity prices and has increased their need to import a range of foods and other products needed by their own population. When human interference with phenotypes that have slowly evolved and adapted to local ecosystemic conditions continues for some time, a danger can be posed to the sustainability of those ecosystems, and the traditional cultures and ways of life built around them.

The genetic modification of domestic animals also raises both concerns of inherent wrongdoing to the rights and welfare of the animals themselves and concerns of risks to human health. The maximization of meat, milk, or egg production has led to genetic modifications in animals that have made them unable to engage in normal repertoires of behavior and left them susceptible to various kinds of infections and disease. Farmers have responded by the widespread use of antibiotics in their herds or flocks, which raises the issue of the evolution of resistant microorganisms.

Genetic Modification in Medicine

Another important motivation for the genetic modification of animals is to make them suitable for medical research that eventually may benefit humans. Selective breeding of rat species for use in the laboratory has been practiced for many decades; quicker and more efficient recombinant methods have more recently come to the fore to produce animals selectively designed to be good models for the study of various kinds of disease. For example, mice have been genetically engineered to model a variety of human diseases including cancers and neurodegeneration.

One of the most interesting and potentially important areas of genetic modification in human medicine is in the field of xenotransplantation. This is the use of organs or tissues from one species in another species. Therapeutic xenotransplantation remains an experimental treatment, but it has a long history that flows from the first use of human organ transplantation. Early experiments with human organ transplantation eventually generated an interest in the use of animals as a source of transplantable tissue. Early experiments involved the attempt to transplant the heart of baboons into human infants; more recently pig livers have been used outside the body to sustain human liver function for short periods of time while a patient who is suffering from liver failure awaits transplant.

Aside from the sacrifice of healthy adult animals that xenotransplantation entails, ethical concerns here mainly focus on the unknown long-term risks. Genetic modification enters into this technology because normally the human body will reject an organ from a non-human source. Bioengineering of the donor animal generally involves the introduction of human genes into an animal to create tissues that are immunologically compatible with humans. These bioengineered (or transgenic) tissues are then harvested and used to replace the tissues or organs that are destroyed, diseased or failing in patients. A decisive objection to animal to human xenotransplantation at this time remains the possibility that viruses indigenous to one species may inadvertently be introduced into the human recipient. This could be very deleterious to the health of the human patient, even fatal, and might threaten others as well if the agent were to prove contagious or infectious.

Xenotransplantation Time Line

1923	First cited xenotransplant: lamb kidney was transplanted into a human who dies nine days later.
1960s	Xenotransplants involving baboon or chimpanzee kidneys.
1960	Transplant experiments with dogs begin.
1963	Dr. Thomas E. Starzl of University of Colorado, Denver, attempts the first liver transplant. The patient dies within a few days.
1964	Cross-species transplantation experiments.
1967	Barnard performs first human heart transplant (patient dies of pneumonia 18 days after transplant).
1967	Dr. Starzl performs the first successful liver transplant. The liver functions for 13 months.
1967–69	More than 100 transplants performed (65% of patients died within three months of the procedure).
1969–74	Dr. Starzl transplants chimpanzee livers into children. The survival time ranges from 1 to 14 days.
1968	Colley and Ross transplant sheep and pig hearts, respectively, into dying human recipients. Both patients died.
1984	"Baby Fae" infant with hypoplastic left heart syndrome receives a baboon heart. She dies 20 days later.
1992	Doctors at Duke University use a pig liver as a bridge to keep two women alive who were awaiting transplants. In one patient, the liver is kept outside the body and hooked to the liver arteries. She survives long enough to receive a human liver. In the other, the pig liver is implanted beside the patient's liver and she lives for 32 hours.
1992	Cazplicki reports an attempt to transplant a pig heart into a human patient using novel immunosupression therapy. The patient died 24 hours later.
1992	Makowka transplants a pig liver into a 26-year old woman dying of acute liver failure. The organ immediately failed.
1997	Robert Pennington receives a "bridge" to transplant extracorporeal pig liver.
1997	More than 250 pig farmers in Malaysia became ill with encephalitis and 101 died. Pigs were identified as the source of the virus.
1997	FDA and its U.K. counterpart call for moratorium on all xenotransplantation.
2003	FDA, NIH, CDC, and HRSA develop guidelines on xenotransplantation and clinical trials can resume.
2000's	Ten Swedish patients with diabetes receive cells from pig pancreas. The cells do not produce insulin as hoped; however, none of the patients become ill from the xenografts.

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