CHAPTER THREE

SOCIETAL CONSTRAINTS; THE INFLUENCE OF GODS, LAWS, NEIGHBORS AND FINANCE

No-one lives in isolation; even lonely people who live by themselves are subject to both the benefits and constraints of their surroundings and the broad society in which they exist. Many of these factors have a marked influence on the medical treatment they chose to, or are allowed to, receive, especially in the context of advanced technologies. I discuss the characteristics and implications of these societal constraints in this chapter. I do so in an order that does not represent their degree of importance but in a sequence that moves from the metaphysical towards the more practical and pragmatic factors.

3.1 ETHICS

3.1.1 General Considerations

As noted earlier, with complex subjects and no clear pathways to solutions, I often write poems to clear my thoughts:

An unwanted new-born baby
Wrapped in today's swaddling clothes
Is left, freezing, on my doorstep overnight
Is it morally acceptable for me to say
Not mine, I don't want it
And leave it to die
Of course not
A moral dilemma?
No, and absolute imperative

I am driving in the dark of night
Late for my flight again
A cyclist, no lights, wobbles off the sidewalk
We collide, all his fault, no one else around, but he is down
Is it morally acceptable for me to drive on
I repeat, not my fault, I will be late
Of course not
A moral dilemma?
No, an absolute imperative

Moral questions, in my humble opinion
Are, at best, rhetoric
We all know the right answer
Even if transiently we are tempted into denial
The wrong decision and action
May live with us forever

I sit on a Supreme Court
Drafting opinions on the interpretation of laws
A child is terminally ill
On life support
Negative quality of life, never to become positive
The parents, through an abundance of love
For their first, and probably only child
Argue for continuation of life
The hospital, insurers and state attorney general
Argue for termination, on the grounds that
To keep the child alive would transgress
A centuries-old constitutional amendment

There are opinions and beliefs, but no right answers
This is the realm of ethics
Not morals, but ethics
Where we are all equal, but none of us right
Who is qualified to be the judge?

David Williams, *No Right Answers*, Unpublished poem, 2018.

The words 'ethics' and 'morals' are often considered to be synonymous; even many well-renowned dictionaries contain this implication, for example defining ethics as a set of moral principles. As the above poem indicates, I hold a different point of view.

Morals refer to sets of generic values that determine what is right and what is wrong. In any one community, this distinction often follows the principles set out in the religions or faiths that dominate that community. This implies that boundaries between moral and immoral actions of behavior will vary throughout the world, and often the differences are more marked between sub-sets of religions than between the religions themselves. For example, virtually all of Muslims in Niger believe that polygamy is morally acceptable, whereas the vast majority in Turkey believe that it is not. Morals are principles that guide individual behavior based on generic community values. More often than not, these moral principles become enshrined in the laws that are intended to lay the foundation for that society.

Ethics concern decision making on issues within a narrow area of activity, usually where no one set of moral principles or established law provides a clear unequivocal answer, especially where both sides of an argument have an equally valid precedent in legal or societal terms, but neither of which accurately and exactly match the situation. This is why this topic is so important for us in the discussion of medical technologies since many of our therapeutic options are so radical and so new that we cannot expect to find the right answers in the history or philosophy books. This area is sometimes referred to as 'bioethics", but the 'bio' prefix adds nothing of value.

There is one important practical reason for differentiating between morals and ethics. I have often found it intriguing that by changing the descriptor of a discussion from 'a moral issue' to 'an ethical matter', a group of individuals feel that they are on higher ground and are emboldened to take decisions because there is 'no right answer'; their decision is as good as anyone else's. This could happen, for example, with a manufacturer of medical devices where, in final validation testing, the product marginally fails a critical test. The consequence (and probably the legal imperative) is that a full failure analysis should be carried out, involving costs and delaying the project. The moral position, based on generic precedent, is quite clear, the analysis must be carried out, otherwise the efficacy or safety of the product, and therefore

the safety of patients, may be compromised. Now raise the level to an ethical debate, solely concerning this one type of device and the position of the company. It may be a ground-breaking innovative device, for which these generic validation tests are not well suited, so maybe no patient will be at risk. The company can ill-afford this costly delay such that this project may have to be abandoned, so no patients will ever benefit from the product. This does happen, and arguments may well be retrospectively included in design files to justify the eventual decision. The real solution, of course, which should have been foreseen together by the heads of R & D and quality assurance, would be to set very precise testing targets for this product and to document ahead of time all possible outcomes of the validation testing and provide reasoned justification for later decision options.

Since ethical matters are influenced by, and have an impact on, so many other factors, I shall only deal with those issues here that are not better discussed elsewhere. Thus, if a dilemma is encountered in medicine that has ethical implications, but which is usually resolved in purely economic terms, it will be discussed there, not here. The same holds for issues that are primarily dealt with under a legal framework, or which are predominantly of religious origin. There is a reason for this. With a specific dilemma, for which no right answer can be found in any relevant place, a governmental of institutional body may be charged with setting a new framework, upon which a decision can be made with some degree of rationality. However, crucial decisions, which set a precedent for years to come, may be based on the text of an overarching Bill of Rights or Constitution which simply cannot be adapted to the world of modern technology. Similarly, the historical precedent may be found in the Christian Bible, the Torah, the Koran or other sacred text. Naturally each society must have a solid framework, and the legal and / or religious basis will have considerable validity.

At the time of writing this section, I was also reading the classic autobiographical novel, 'Walden' by Henry David Thoreau[1], not thinking that it had any connectivity with the task on which I was working. The storyteller built a rudimentary cottage in a wood in Massachusetts, quite close to the Walden Pond, where he spent much time fishing and reflecting on life. While considering the laws of nature, he observed that '*we know only a few laws, and our result is vitiated not by any confusion or irregularity in nature, but by our ignorance of essential elements in the calculation*'. This comment arose from his detailed analysis of the topography of the pond; it had several coves, which had bars across their mouths, with deep water within them such that '*the bay seemed to be an expansion of water within the land not only horizontally but also vertically*'. Sand bars move over a period of time, and that expanse of water takes on different appearances depending on time and also the position from which it is observed.

The critical point here, and certainly the one which attracted my attention, was Thoreau's deduction that *'what I have observed of the pond is no less true in ethics'*. I shall partly quote and partly paraphrase Thoreau's explanation:

> *"….rules draw lines through the length and breadth of a man's particular daily behaviors and waves of life into his coves and inlets, and where they intersect will be the height or depth of his character…..If he is surrounded by mountainous circumstances, whose peaks overshadow and are reflected in his bosom, they suggest a corresponding depth in him. But a low and smooth shore proves him shallow on that side…. There is a bar across the entrance to every cove, or particular inclination; each is our harbor for a season, in which we are detained and partially land-locked. When this bar is gradually increased by storms, tides or currents, or there is a subsistence of the waters, so that it reaches to the surface, that which was at first but an inclination in the shore in which a thought was harbored becomes an individual lake, cut off from the ocean, wherein the thought secures its own conditions, changes, perhaps, from salt to fresh, becomes a sweet sea, dead sea, or marsh".*

[1] Henry David Thoreau, "*Walden*", Oxford World Classics, 1999, ISBN 978-0-19-953806-5.

In other words, ethical positions can change, with time, perspective, and evolving environments. If there is no right answer, the balance between rightness and wrongness is not a fixed phenomenon.

3.1.2 Reproductive Technologies

During the Covid-19 Pandemic in 2020, when travel and both social and professional interactions were very limited, I spent some time writing a collection of sonnets that focused on the history of medicine. These are contained in the Poetry and Arts section of this website, but I include a few relevant poems in this text. With each poem I wrote a short 'backstory' to explain the sometimes-opaque message. Here is the first, which concerns the reproductive technology of *in vitro* fertilization.

> Backstory
> There are several definitions of infertility, one common epidemiological version indicating that it is 'women of reproductive age at risk of becoming pregnant who report unsuccessfully trying for a pregnancy for more than two years'. It is estimated that there are 50 million couples world-wide in this situation. Until quite recently, very little, at least from a medical perspective, could be done to help them.
>
> Robert Edwards, a Yorkshireman, was born in 1925. He took a science degree in Bangor, Wales, and moved to Edinburgh to work in the areas of genetics and reproduction. Between 1952 and 1957 he generated haploid, triploid and aneuploid mouse embryos and studied their potential for development; for this, he needed to manipulate the chromosomal composition of eggs, spermatozoa and embryos. He described the timed sequence of egg chromosomal maturation events that led up to ovulation. This led to his interest in *in vitro* fertilization, which he pursued after moving to Cambridge. He struggled with the complexities of both science and ethics; eventually he met Patrick Steptoe, an obstetrician and the two worked on IVF until, in a pivotal paper in Nature in 1968, they demonstrated IVF in humans for the first time. For 10 years the British establishment was unwilling to engage seriously in ethical debates. However, the final validation of IVF came in 1978 with the birth of Louise Brown. The technique was then accepted world-wide, with several million IVF births recorded to date; Sir Robert Edwards was awarded a Nobel Prize in 2010.
>
> *The tortuous path that both gametes trace*
> *To meet within the fallopian tube*
> *Is well-known to science and the embrace*
> *Of fertilization's own Rubik's cube*
> *Where all pieces have to be in their place*
> *For sperm to have a chance to penetrate*
> *An ovum, a zygote to form in space*
> *Embryo attaches to then gestate*
> *For millions of couples the cube resists*
> *No twisting or spinning will ever win*
> *So take the gametes outside for their trysts*
> *A baby is formed, just to fool Darwin*
> *IVF delivers what nature could not*
> *A new life for couples, their own Camelot*
>
> **David Williams, *Fertile Glasses, in "A History of Medicine in Sonnets", Unpublished, 2020***

At the time of the introduction of IVF, the ethical aspects were widely discussed. These were brought sharply into focus by the cover illustration in Time magazine in July 1978, and a comparison with a section of Michelangelo, 'The Creation of Adam' on the ceiling of the Sistine Chapel.

Figure 3.1, On the left, the cover of Time Magazine in July 1978, at the time of the first human experience of IVF and on the right, a section of Michelangelo 'The Creation of Adam' in the Sistine Chapel.

As noted in the Prologue, I make no attempt to discuss clinical techniques designed to influence reproduction unless they specifically involve medical technologies. There are, obviously, some gray areas here, within which I tread very carefully. I will mention these in relation to the assistance in fertility / reproduction, the avoidance of conception and *in utero* modification and gene editing. Many of the ethical issues that I mention (just briefly) were covered in an excellent collection of essays in the AMA Journal of Ethics in 2012[2].

It is also worth considering, at the outset of this discussion, a few broader issues within the ethical (and moral) perspectives of human reproductive medicine, and I use the Turner and McLindon 2018 paper in The Linacre Quarterly for background here[3]. At the center of the major theological / ethical debates are the semantics associated with conception. The long-standing view is that of essential biology, where conception refers to fertilization of an oocyte by a spermatozoon resulting in a zygote. It has suited some views to change this definition to that of conception beginning with the implantation of an embryo in a woman. Within assisted reproduction technologies, fertility has been equated with '*the capacity to establish a clinical pregnancy, which allows for extracorporeal manipulation of gametes and fertilization'*. It has been the Catholic Church that has dominated the ethical discussions, and indeed mandates, with respect to fertility control in general[4] and to assisted reproduction technologies in particular[5].

[2] Virtual Mentor, Ethical Issues in Family Planning. *AMA Journal of Ethics,* 2012;14(2):89-180.
[3] Turner JV, McLindon LA, Bioethical and moral perspectives in human reproductive medicine, *The Linacre Quarterly*, 2018;85(4):385-398. doi:10.1177/0024363918816697.
[4] The Supreme Pontiff, Paul VI, Encyclical Letter "*Humanae Vitae*:. 25th July 1968, Libereia Editrica Vaticano.
[5] Congregation for the Doctrine of Faith, "*Dignitas Personae, on Certain Bioethical Questions*," Sept 8th 2008.

According to this Church, technical intervention in the procreative process should respect three essential elements; first, the right to life and physical integrity of the embryo from the moment of conception, secondly, the right to become a father or mother only through one's spouse in marriage, and thirdly that procreation should be '*the fruit of the conjugal act specific to the love between spouse*s'. The problem here, obviously, is that any intervention that facilitates the conjugal act in reaching its end is permitted, but any action that substitutes the conjugal act is to be excluded. At a time when the rupture of relationships and a '*lowering of sexual standard*s' are accepted facts of life, the fundamental position espoused in this present text, that in ethics there is no absolute right answer, is clearly demonstrated,

I do not consider here any techniques relating to reproduction that are entirely destructive rather than reconstructive, for example hysterectomies, and I do not cover any methods that are based on chemical, biochemical or pharmacological principles, such as birth-control medication. There are many ways, however, in which sperm can be modified after ejection / removal from the male or the environment and / or the physiology of a fetus can be changed before a child is born.

3.1.2 Assisted Reproductive Technologies

I deal with this only very briefly, for obvious reasons.

There are four techniques that are employed in assisted reproduction, although there are many common features; During *in vitro* fertilization, eggs are retrieved from the woman and fertilized with sperm in a petri dish. The resulting embryo is placed back into the uterus. The woman usually takes fertility drugs to ensure she ovulates on a predictable timeline and to encourage her body to produce multiple extra eggs. Secondly, with intrauterine insemination the egg is fertilized inside a woman's uterus. This works best for women with unexplained infertility, or when the sperm has issues of low mobility, but sometimes it is used where there is a chemical mismatch between the man's semen and vaginal fluids. Thirdly, an intrafallopian transfer fertilizes the egg inside the woman's fallopian tube, used especially when the woman has an issue with her fallopian tube, such as a blocked tube. A gamete intrafallopian transfer involves both sperm and eggs, often preferred because of religious or ethical beliefs dictating that fertilization should occur inside the body. A zygote intrafallopian transfer is similar to IVF, but the embryos are deposited into the fallopian tube. Finally, intracytoplasmic sperm injection, ISI, removes one or more eggs, following which a mature egg is injected with a single healthy sperm. When the eggs develop normally, they are transferred back to the woman's body. ISI works best when there are serious sperm issues as it allows selection of the healthiest sperm.

This area of medical technology, although only marginally relevant to reconstructive medicine, is rife with ethical, legal, and spiritual aspects. I will refer to a recent paper by Tam on reproductive justice in assisted technologies that covers many of these issues[6], and a few other relevant opinions. The question of justice in reproductive technologies has been raised in the context of the focus on infertility / low fertility in heterosexual couples and the much lower impact in so-called LGBTQ individuals and couples. According to Tam, there is ample evidence to support the view that regulations seek to control the reproductive capacities of marginalized communities, while empowering accessibility and upholding white supremacy and heteronormality. Long held views, and indeed biases, influence attitudes to assisted reproductive technologies in many faith and religious communities, even though the availability of these technologies far post-date the origin of the fundamental beliefs. Saniei and Kargur have discussed disparities in the Muslim world in this respect[7]. While the Sunni sect bans all forms of third-party egg,

[6] Tam M, Queering reproductive access: reproductive justice in assisted reproductive technologies, *Reproductive Health,* 2021;18:164. doi:10.1186/s12978-021-01214-8.
[7] Saniei M and Karger M. Modern assisted reproductive technologies and bioethics in the Islamic context, *Theology and Science*, 2021;19(2):146-154. doi:10.1080/14746700.2021.1910914.

sperm, or embryo donation due to matters of kinship and lineage, with prohibition of surrogacy and sex selection[8], in the Shi'a sect, virtually all forms of assisted reproduction are permitted (except for human cloning) and third-party gametes and embryo donation are allowed.

The vexed questions of how couples live with infertility has been dealt with recently by Romeiro *et al*[9]; it is worth while looking at the disadvantages of not using the opportunities that these technologies can provide. As a final point here, in a field that is moving so fast, the 2020 review of recent books on these subjects by Ross and Moll is also valuable[10].

3.1.2.2 Technologies for the Avoidance of Conception

Obviously, the only technologies to be covered here are those where either female of male bodies are reconstructed in order to prevent completion of some critical part of the conception pathway.

3.1.2.2.1 The Female Body

Birth control methods for females include those that are temporary (e.g., those that prevent sperm from reaching the egg through barrier or hormonal techniques) or permanent. It is the latter group with which we are concerned here, these widely being referred to as sterilization methods, these involving permanent reorganization of tissues and structure. It should be noted that some practitioners and authors, for example Micks and Jensen,[11] object to the term 'sterilization', since this may be politically charged and medically inaccurate, preferring the term 'permanent contraception'.

Sterilization is achieved by preventing eggs, released from an ovary during ovulation, from meeting sperm within the fallopian tubes, this being achieved by blockage or the fallopian tubes, or their total removal from the body. There are three ways in which this could be done, tubal occlusion, salpingectomy or hysteroscopic sterilization.

Interruption of tubal patency through closure of the tubal lumen can be achieved by cutting them and tying them (known as partial salpingectomy), blocking them mechanically through the use of clips or rings (such as Hulka or Filshie clips[12]), by applying electric currents (electrocoagulation), or by chemical irritation. Apart from the latter methods, most have widespread acceptance with respect to safety and efficacy[13]. The majority of tubal ligations are performed post-partum, especially following cesarean section[14]. Outside of the post-partum period, so-called 'interval ligation' may be performed laparoscopically, either with silicone rubber bands, titanium clips or electrocoagulation; this is popular in low-resource countries.

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[8] Chamsi-Pasha H and Ali Albar M, Assisted reproductive technology: Islamic Sunni perspective, *Human Fertility*, 2015;18(2):107-12. doi:10,3109/14647273.2014.997810.

[9] Romeiro J, Caldeira S, Briady V, *et al*. Spiritual aspects of living with infertility: A synthesis of qualitative studies, *Journal of Clinical Nursing*, 2017;26:3917-3935. doi:10.1111/jocn.13813.

[10] Ross FC and Moll T, Assisted reproduction: Politics, ethics and anthropological futures, *Medical Anthropology, 2020;39(6):553-562. doi:10.1080/01459740.2019.1695130.*

[11] Micks EA and Jensen JT, Permanent contraception for women, *Women's Health,* 2015;11(6):769-77. doi:10.2217/whe.15.69

[12] Dominik R, Gates D, Sokal D, *et al*, Two randomized controlled trials comparing the Hulka and Filshie Clips for tubal sterilization, *Contraception*, 2000;62(4):169-75. doi: 10.1016/s0010-7824(00)00166-9.

[13] Lawrie TA, Kulier R and Nardin M, Techniques for the interruption of tubal patency for female sterilization, *Cochrane Database of Systematic Reviews,* 2015;9:Art CD003024, doi:10,1002/14651858.CD003034.pub3.

[14] Patil E and Jensen JT, Update on permanent contraception options for women, C*urrent Opinions in Obstetrics and Gynecology,* 2015;27(6):465-70. doi:10.1097/CGO.0000000000000213.

A major alternative to tubal ligation is salpingectomy, which is the total removal of the fallopian tubes. There is an added factor here; up to 70% of ovarian cancers arise from the fallopian tubes and since these constitute the most serious gynecological malignancy, reduction of risk is a prime consideration[15]. A further approach was introduced in the USA in 2002, involving so-called hysteroscopic tubal occlusion, specifically using a commercial medical device, Essure®. This has a nickel-titanium outer coil and a stainless steel inner coil, wrapped in polyethylene terephthalate fibers. A disposable introducer allows the positioning of the coil into the proximal part of the fallopian tube. This could be done, bilaterally, under hysteroscopic guidance with only local anesthesia. However, regulatory pressure caused the device to be removed from the market around 2015, apparently because of adverse tissue responses to the coils[16]. This matter is discussed elsewhere in this book because of implications for biocompatibility and the influence of pressure from social media on decision making processes in commercial aspects of medical devices.

3.1.2.2.2 The Male Body

Options, and techniques, are much simpler here, being associated with the vasectomy procedure. With conventional vasectomy, each of the two vas deferens, one for each testicle are cut, leaving a short gap between the two ends, which are tied off with a suture. When each vas deferens has been cut, sperm can no longer reach the semen or leave the body. In some cases, a so-called 'No-Scalpel Vasectomy' is used where each vas deferens is lifted out from the scrotum and clamped; a small hole in the skin allows each tube to be lifted out, cut and sealed. It is possible to perform a vasectomy reversal, either by a vasovasostomy, where the severed ends of each tube are re-joined, or by a vasoepididymostomy, in which the vas deferens is directly attached to the small organ (epididymis) at the back of each testicle that holds sperm.

3.1.2.3 Preconception and In Utero Modification

It has been possible for several years to undertake, through flow cytometry techniques, the sorting of human sperm derived from a male prior to implantation in a female[17]. The intensity of the fluorescence emitted by the DNA of chromosomally normal, fluorescently stained sperm differs between X- and Y-chromosomes. X-chromosome-bearing sperm have about 3% more total DNA than Y-bearing sperm. In sperm stained with a DNA specific fluorochrome, this allows the differentiation of X- from Y-bearing sperm such that enriched populations of X- or Y-bearing sperm may be generated and used. A child so conceived will be of a particular sex, providing a preconception option for parents. This may be because they wishing to reduce the risk of sex-linked and sex-limited disease risk in the child or to balance the sex ratio among their children.

While few would argue with the rationale for sex determination to prevent serious genetic disorders, the option of sex selection unrelated to the medical welfare of the child clearly has an ethical dimension. This is a very good example of the principles of ethical consideration I mentioned at the beginning of this section, where there is no obvious right or wrong answer. In the USA, this dichotomy may be seen by the FDA's position that sex selection should not be available for parents to balance their families, whereas the Ethics Committee of the American Society for Reproductive Medicine has oscillated on the matter, the

[15] Dilley SE, Straughn and Leath CA, The evolution of and evidence for opportunistic salpingectomy, *Obstetrics and Gynecology,* 2017;130:814-24. doi:10.1097/AOG.000000000002243.

[16] Walter JR, Ghobadi CW, Hayman E, *et al,* Hysteroscopic sterilization with Essure, *Obstetrics and Gynecology*, 2017;129(1):10-9. doi:10.1097/AOC0000000000001796.

[17] Karabinus DS, Marazzo DP, Stern HJ, *et al,* The effectiveness of flow cytometric sorting of human sperm (MicroSort) for influencing a child's sex. *Reproductive Biology and Endocrinology*. 2014;12:106. doi:10.1186/1477-7827-12-106.

latest commentary[18] being that there is no consensus; they recognize that arguments regarding patient autonomy and reproductive liberty have been offered in support of the practice, while risks, including gender bias, sex stereotyping and nonacceptance of offspring, efforts to guard against coercion, and issues of justice all raise legitimate concerns. It is not hard to see the positions here being extended to those of commodification discussed elsewhere in this section.

3.1.2.4 Regenerative Medicine Techniques for Genital Traumatic Injuries

The majority of penetrating injuries to the male genitalia are associated with gunshot wounds and high velocity shrapnel[19]. This has become a major issue in military medicine since so many men are injured by explosive devices but survive because of the advances made in their treatment in battlefield settings. One consequence of this is the need for psychiatric care related to the sexual health of these individuals[20]. This is also an area where the potential for tissue engineering / regenerative medicine techniques for reconstruction has been much discussed[21], including the use of stem cells[22], although human applications are not yet possible.

3.1.2.5 Functional and Cosmetic Reconstruction of Sexual Organs and Structures

Reconstruction of sexual organs, which can be performed for either functional or aesthetic purposes, is a clinical practice of increasing commonality, both for males[23] and females[24]. These procedures are discussed later in this book in relation to specific anatomical structures, but it should be noted here that, especially for males, the requirements for genital reconstruction, especially penile enlargement, are usually driven by reasons of self-confidence and mental attitude.

3.1.3 Transgender Issues

This is something that is rarely taught, or even considered, within the space of reconstructive surgery, but when you reflect on the enormity, physically, psychologically, spiritually, and legally, of the subject of gender realignment, there can hardly seem to be a more profound challenge, perhaps on a par with face transplantation. As discussed by Aurelie Athan[25], models of psychosocial identity started to be challenged in the mid 20th century, especially with respect to the biased assumptions of what were considered to be normal and acceptable. Power hierarchies excluded people from accessing equal opportunities, and disparities, initially focusing on poverty, were created that led to marginalized groups.

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[18] Ethics Committee of the American Society for Reproductive Medicine, Use of reproductive technology for sex skeleton for non-medical reasons, *Fertility Sterility,* 2015;103(6):1418. doi:10.1016/j.fertnstert.2015.03.035.

[19] Goldman C, Shaw N, du Plessis D, *et al,* Gunshot wounds to the penis and scrotum: a narrative review of management in civilian and military settings, *Translational Andrology and Urology*, 2021;10(6):2596-608. doi;10.21037/tau-20-1175.

[20] Tepper MS, Sexual healthcare for wounded warriors with serious combat-related injuries and disabilities, *Sexual Medicine Reviews*, 2014;2(2):64-74. doi:10.1002/smrj.24.

[21] Andrew TW, Kanapathy M, Murugesan L, *et al*, Towards clinical application of tissue engineering for erectile penile regeneration, *Nature Reviews Urology,* 2019;16:734-44. doi;10.1038/s41505-019—0246-7.

[22] Ude CC, Miskon A, Idrus RBH, *et al,* Application of stem cells in tissue engineering for defense medicine, *Military Medical Research*, 2018;5:7. doi:10.1086/s40779-018-0154-9.

[23] Alter GJ, Salgado CJ and Chim H, Aesthetic surgery of the male genitalia, *Seminars in Plastic Surge*ry, 2011;25:189-95. doi:10.1055/s-0031-1281488.

[24] Magon N and Alinsod R, Female cosmetic genital surgery, *Journal of Obstetrics and Gynecology of India,* 2017;67(10:15-9. doi:10.1007/s13224-016-0930-y.

[25] Athan AM, Reproductive identity: An emerging concept, *American Psychology*, 2020;74(4):445-56. doi:10.1016/jfertstert.2015.03.035.

More recently, societal views on sex and gender have taken an increasingly important position in this discussion. Traditionally, society has tended to view sex as binary, where individuals are based on stereotypes typically assigned to physical characteristics associated with 'male' and 'female'[26]. However, a growing number of individuals self-identify as gender non-conforming. Definitions are evolving here, but now the term 'cisgender' is used to describe an individual whose assigned biological sex aligns with their expected binary gender identity, while the converse, 'transgender', denotes someone whose gender identity does not align with the socially expected identity according to their sex assigned at birth. While for some, individual's transgender feelings are accepted without too much trouble, for many that is not the case and they will experience 'gender dysphoria' (recently re-named from gender disorder), which is a recognized condition of psychological distress. In many communities (e.g., the USA) a professional diagnosis of gender dysphoria is necessary before any medical or surgical procedure associated with 'gender affirmation' techniques can be applied.

In terms of reconstruction of the body, gender dysphoria may suggest that surgical procedures could be appropriate as part of the process of changing the gender of the individual. Of course, there are elements of social affirmation (changing names etc.), legal affirmation (changing official documentation etc.) and non-invasive medical affirmation (e.g., gender affirming hormones), but for many it is the obvious physical and sexual features that must be addressed and changed. For the sake of clarity here, a transgender man (transmasculine) is one who has transitioned their identity, and possibility their body, from woman to man, while a transgender woman (transfeminine) has transitioned their identity, and possibility their body, from man to woman.

I deal here first with the clinical aspects of gender affirmation surgery and then some of the societal, spiritual, and ethical features.

3.1.3.1 Gender Affirmation Surgery

Up to 1.3% of the population of the USA have gender dysphoria[27], with a higher prevalence in natal males than in natal females. An increasing number of such people are now availing themselves of gender-related genitourinary surgery[28].

3.1.3.1.1 Transfeminine Surgery

This surgery may involve:

- Vaginoplasty, either full depth or shallow: creation of a vagina
- Orchiectomy: removal of testicle
- Penile disassembly: removal of penis
- Creation of neovaginal cavity, between the rectum and urogenital structures
- Labiaplasty; alteration of size of labia minora
- Clitoroplasty; creation of a clitoris
- Urethral reconstruction

[26] Palmer BF and Clegg DJ, A universally accepted definition of gender will positively impact societal understanding, acceptance and appropriateness of health care, *Mayo Clin Proc,* 2020;95(10):2235-43. doi:10.1016/j.mayocp.2020.01.031.

[27] Zucker KJ, Epidemiology of gender dysphoria and transgender identity, *Sexual Health*, 20017;14:404-11. doi:10.1071/SH17067.

[28] Chen ML, Reyblat P, Poh MM *et al*, Overview of surgical techniques in gender-affirming genital surgery, *Translational Andrology and Urology*, 2019;8(3):191-208. doi:10.21037/tau.2019.06.19.

Although techniques do vary, the vaginoplasty is usually achieved with a penile inversion method, wherein a penile skin flap is supplemented with a scrotal skin graft, which is tubularized around a dilator, to line the neovagina. As can be imagined, this whole process requires meticulous attention to detail, especially hemostasis, highly accurate positioning and tensioning of the grafts. There are several potential complications, including vaginal stenosis, rectoneovaginal fistulae, urethral stricture, and clitoral exposure.

3.1.3.1.2 Transmasculine surgery

There are two major alternative procedures for gender-affirming surgery for transgender men.

Metoidioplasty is the creation of a phallus from the hormonally enlarged clitoris; a minimum of a year on testosterone therapy is required. The clitoral ligaments are detached, which allows it to lengthen and drop into a reasonably normal anatomic position. This can be done with or without urethral lengthening. It is usually performed with vaginectomy, the excision of the vaginal mucosa, and colpocleisis, the suturing of anterior and posterior walls of the vagina.

Phalloplasty, which has become less popular than metoidioplasty in recent years, is the construction of a neophallus. This is usually achieved by using radial forearm free flap grafting methods along with vaginectomy, urethroplasty, scrotoplasty and perineal reconstruction. This requires several procedures and may lead to conspicuous donor site scaring. Normally patients opting for phalloplasty rather than metoidioplasty require a more proportionally sized phallus with relevant sensation, the ability to urinate standing and, eventually, penetrative sexual function. The latter function is usually achieved by means of a penile prosthesis[29]. First attempts involved transplants of cartilage or bone, but these were abandoned because of persistent rigidity and pressure necrosis. The alternatives are variations on hydraulic prostheses, in which one or two cylinders are implanted in the neopenis, that are connected to a fluid reservoir and pump, for activation and deactivation by the individual. Most patients have subsequent surgery for the implantation of testicular prostheses, made of silicone elastomers, that are placed in a neoscrotum. There are many possible complications with these techniques and devices, and currently they are far from satisfactory.

3.1.3.1.3 Surgery for intersex

A related, but somewhat different, aspect is that of intersex. This refers to situations where individuals are born with ambiguous genitalia. For example, females may be born with inguinal hernias that contain testes, or a large clitoris that looks, and perhaps functions, as a penis. These conditions may not be obvious at birth – they may develop later or be part of a major or generalized anomaly and not fully recognized. At one stage these individuals were described as pseudohermaphrodites, but this use has been discontinued for obvious reasons.

The management of intersex individuals is usually a complex matter. In the simpler cases, for example in congenital adrenal hyperplasia, a condition affecting genes involved in the production of steroid hormones, the individual may have a female karyotype with normal uterus and ovaries and is potentially fertile, so that female gender assignment is usually followed, even if testes are present. In other situations, especially in cases of partial androgen insensitivity, a male fetus may not respond to male hormones, which can result in wide-ranging genitalia abnormalities. Clinicians and parents usually aim to choose the gender that has the best prognosis with respect to sexual and reproductive function and where the physical appearance looks most normal. Several decades ago, it was common practice to perform genital surgery on individuals to 'enhance normality', including clitorectomy, but many of these

[29] Kang A, Aizen JM, Cohen AJ, *et al*, Techniques and considerations of prosthetic surgery after phalloplasty in the transgender male, *Translational Andrology and Urology*, 2019; 8(3):273-82. doi:10.21037/tau.2019.06.02.

procedures are no longer performed[30]. Most forms of congenital adrenal hyperplasia are now treated with hormones, but seriously mis-shaped genitals can be modified by surgery, especially in so-called feminizing genitoplasty methods such vaginoplasty. These procedures do carry risks, especially when complex grafting is required for construction of the neovagina, and decisions on the need for such surgery are usually deferred until adolescence or later, when the patient is able to make a sound informed decision.

3.1.3.2 Societal and Spiritual Aspects of Transgender Issues and Gender Affirmation Surgery

The Pew Research Center has recently published several reports on the views of the public on transgender matters[31] and it is clear that there are widely different positions. White evangelical Protestants (84%) are most likely to say that gender is determined by sex at birth. Catholics are divided, with 46% saying it is possible for someone to be of a gender different from their sex at birth; 40% of all Christians believe that society has gone too far in accepting transgender people. In the USA there is, unsurprisingly, a marked difference among politicians; while President Obama issued a regulation in 2016 that required doctors to perform 'gender transition operations' on any patient, regardless of age, any refusing doctor facing severe consequence, the following administration invalidating this rule, the position still being under discussion. As I write this section late in 2020, the New England Journal of Medicine published a perspectives paper[32] that made it clear that uninformed, partisan officials were rejecting any interpretation of sex-nondiscrimination laws as providing protection to transgender (and other LGBQ) individuals. Trans and gender-diverse people already face disparities in health care, enhanced by '*pervasive structural, interpersonal and individual-level stigma that prevents access to effective and affirming health services*'; this is exacerbated when the individuals belong to other minority groups, especially with respect to race and color.

The majority of specialist centers around the world follow the recommendations of The World Professional Association of Transgender Health[33]. Obviously, this has not always been the case; the evolution of societal views and practices in this matter is rather difficult to trace since the subject has been a taboo in most civilizations throughout most of history.

3.1.3.2.1 Androgyny and shamanism

Interestingly, one of the oldest examples of the recognition of gender issues rests within shamanism and some related cultures[34]. Shamans encounter androgynous (i.e., of indeterminant sex) and bisexual (i.e., being attracted to both males and females) spirit guides in their initiation journeys, exposing themselves to multiple dimensions of existence, especially to their liminal characteristic that confers the ability to act as an interpreter of spiritual matters. As noted below, the transcendence of male and female forces is incorporated in many mystical traditions, but it is in shamanism that androgynous practices are most explicit. The androgyne, the half male – half female creature (from the Greek 'andros' and 'gune') is a symbol in shamanic cultures and is usually given a very clear figurative expression. The androgyne is such a powerful symbol because it can bridge relative and ultimate experiences, primarily by the person

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[30] Creighton S, Surgery for Intersex, *Journal of the Royal Society of Medicine,* 2001;94:218-20. doi:10.1177/01410768909400505.

[31] Pew Research Center, Report "Views of transgender issues divide along religious lines", Nov 27th 2017; Report "Republicans, Democrats have starkly different views on transgender issues", Nov 8th 2017.

[32] Malina S, Warbelow S, Radix AE, Two steps back – rescinding transgender health protections in risky times, *New England Journal of Medicine*. 2020;383:e116. doi:10.1056/NEJMp2024745.

[33] WPATH, The World Professional Association for Transgender Health, "Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th Version 2011.

[34] Cowan T, Fire in the Head; Shamanism and the Celtic Spirit, Harper, San Francisco, 1993.

engaging in any sort of androgynous behavior, especially during ritual and spiritual practice. Shamans mediate between the material world and the spirit world, being best achieved by the androgyne shaman.

The ambisexual shaman is a healer and ritual leader. Language has been modified to reflect this ambisexual nature. Alternative gender types have been termed 'third and fourth genders', which helps in understanding the role of androgyny in this different mental reality. In some groups this has now been replaced by the concept of 'two spirit', which is a range of manifestation of the gender continuum, neither strictly male nor female. Physical anatomy does not necessarily bind an individual to one experiential existence or another**.** Different shamanic cultures show a greater diversity of sexual behaviors, which are accepted through the spiritual and shamanic powers attributed to them. It is usually through a distinct initiation that someone becomes a 'two spirit' shaman; the metamorphosis may start early in infancy, when the child's special abilities are recognized. The male initiates often have to cross-dress, and in some cases a sub-incision is made to symbolize a vagina. This merging of the male-female dichotomy is central to shamanic cultures; being able to spiritually combine the forces of male and female is seen as essential for one who can then bridge other polarities.

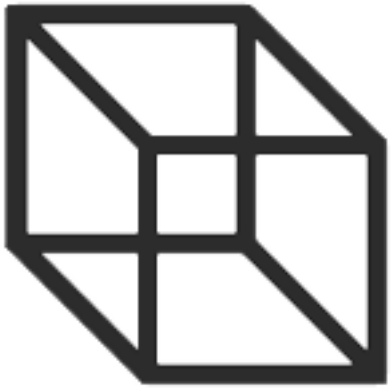

Figure 3.2 Androgyny: The Necker Cube is an optical illusion first proposed by Swiss crystallographer Louis Albert Necker in 1832. It is a two-dimensional line drawing that may be interpreted as a three-dimensional cube in one of two orientations. The cube is often presented as a symbol of ambiguity and an illustration of the human brain's ability to switch between two states of perception when presented with an ambiguous image. It represents androgyny.

3.1.3.2.2 Transgender and androgyny beliefs in different cultures

Not surprisingly, the spectrum of beliefs about gender issues in different cultures, and religious sects, is very wide.

The concept of gender is an essential element of Chinese philosophy. Notions of 'yin' and 'yang' involve correlative aspects of dark and light and of female and male. These notions, which recognize the necessity of interplay between these different forces, established, several millennia ago, a comprehensively gendered view of the world. The most influential, albeit opposing perspectives of gender belonged to the Confucian and Daoist. Confucianism emphasizes *yang*'s dominant, male-related characteristics, whereas Daoism finds value in *yin*'s subordinate, female characteristics. Nevertheless, both see the opposing qualities of *yin* and *yang* as integral to the whole, which complement one another. The genders, in terms of social roles, are not defined absolutely or theoretically, but rather through the

mutually reciprocal, physical, relationship between male and female. In both cases, transgender concepts are not relevant and indeed are considered to usurp the established gender roles.

Interestingly, and essentially parenthetically, transgender issues in China have been most obvious in theatrical arts, especially in Peking, and to a lesser extent, Cantonese, opera[35] in the context of cross-dressing. The origins of cross-dressing in China can be found in the tale of Mulan, recently made into a film in the USA. Mulan's story is a folk ballad dating back to the Northern Dynasties in China which tells the story of a girl who dresses as a man and joins the army, taking her father's place because she has no elder brother to fulfil that role. After years of military campaign, she returns with honor and the emperor's gifts. Her family prepare a feast to welcome her home. When she changes her clothes, her fellow soldiers are shocked since, after fighting side-by-side, they were not aware that Mulan is actually a woman.

Figure 3.3. Painting of Hua Mulan.

Much later, during the Ming and Qing dynasties, cross-dressing became quite popular, both in everyday life but especially on stage. Most cross-dressing cases are of actresses playing male roles, the innate constraints of male voices making it difficult for them to imitate female voices. The cross-dressing blurs the boundaries between the two genders; with the complex physical and mental aspects of performance, adopting a vocal representation of the opposite gender involves a misapprehension of the performer's

[35] Kar Yue Chan, Cross-dressing and gendered voice representation in Cantonese Opera, *Comparative Literature: East & West,* 2019;3(1): 1-14. doi:10.1080/25723618.2019.1615727.

real-life gender and there is a degree of gender-boundary confusion and flexibility within these operatic performances. Discussion and presentation of all aspects of sexuality was suppressed during the Mao era, but operas have continued to be popular and, even though transgender characteristics are still considered to be 'disorders', an increasing number of individuals declare themselves as gender non-conforming (perhaps numbered in millions). Gender affirmation surgery is possible, although very expensive and the rights of individuals are now being protected by new anti-discrimination laws. The operatic cross-dressing appears to have played a subtle role in this transformation.

In Greek mythology, there were originally three kinds of humans: male, descended from the sun; female, descended from the earth; and androgynous, with both male and female elements, derived from the moon. All were completely round, with four arms and four legs and two identical faces on opposite sides of a head. They walked both forwards and backwards and ran by turning cartwheels on their eight limbs. Because of their power, Zeus and Apollo devised methods to cut them into two, turned their heads to make them face towards their wounds, using their skin to cover up the wound, tied together at the navel. After this punishment, humans longed for their other half so much that they searched for it all over. When they found it, they held on very tightly and did not let go. Zeus took pity on them and moved their genitals to the front so that those who were previously androgynous could procreate, and those who were previously male could obtain satisfaction. This was deduced as the origin of desire for other human beings; those who desire members of the opposite sex were previously androgynous, whereas men who desire men and women who desire women were previously male or female.

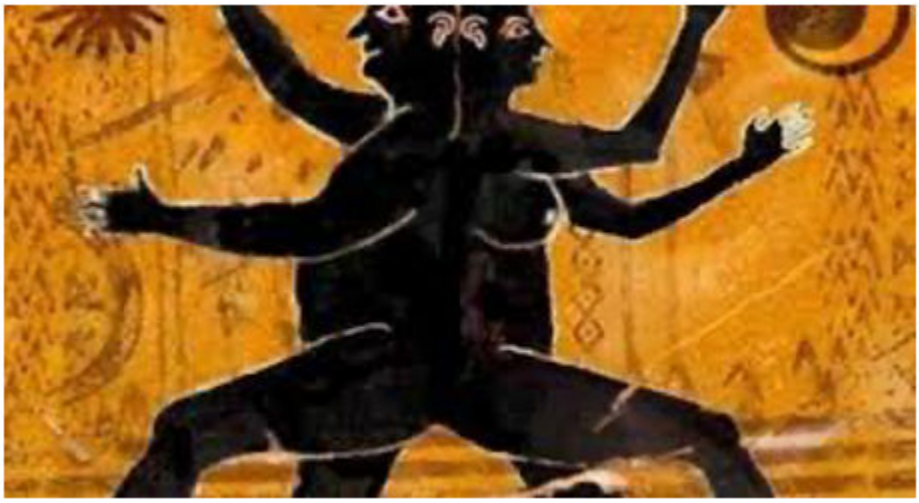

Figure 3.4. Androgyne; in Greek mythology.

The implications of this mythos were taken up by Aristophanes and his contribution to Plato's *Symposium*[36], especially on the power of Eros is a significant influential literary text on hermaphrodite/androgynous bodies. This alleged mythos explains both homosexual and heterosexual desire, and the figure of the Hermaphrodite features prominently in sexual desire; for Aristophanes, heterosexual desire can be explained as a result of the splitting of the androgyne.

[36] Dover K, (Ed.), Plato Symposium, Cambridge Greek and Latin Classics, 1980. ISBN 0521295238

Figure 3.5 Ardhanarishvara, In the Art Museum of Chicago.

Similar androgyne splitting and fusion characteristics are seen in Hindu mythology originating around the first century AD. A composite form of Shiva and Shakti comprises the Ardhanarishvara, the '*God who is half-woman'*, which represents the reconciliation and harmonization of opposites, including both father and mother, and spiritual and materialistic dichotomies. Shiva represents Purush, the male and Shakti represents Prakriti, the female principle. They are constantly drawn to one another and fuse with each other, that is believed to generate creation and ultimately the universe. The left side of the body is associated with the heart and feminine attributes such as intuition and creativity, while the right side is associated with the brain and masculine characteristics such as methodical thought and gallantry. In most representations, the right half is usually Shiva and the left, Shakti. The male half is depicted with masculine *features of muscular chest and thighs*. *Some* images may portray the male aspect half-nude and ithyphallic. The female half of has a curvier body with exaggerated breasts and hips.

In Africa the situation is, and indeed has been for centuries, very mixed. In many rural areas, where traditional healers play prominent roles alongside doctors and nurses, babies born with ambiguous genitalia may be killed by parents; intersex infanticide occurs because of beliefs that this condition brings bad omens[37]. Conversely, Africa has a history of gender non-conformity and transgender behavior that is deeply embedded within several ethnic groups. For example, within the Dagaaba tribe of Ghana and the Ivory Coast, gender identity may not be dependent upon sexual anatomy, as one who is physically male can vibrate female energy. The Igbo of Nigeria assign gender at around the age 5 and the Mbuti do not designate gender until after puberty. The Dogon tribe of Mali generally maintain that the perfect human being is androgynous. Lugbara peoples of Democratic Republic of the Congo still conduct spiritual ceremonies with transgender priests where female-to-male priests co-exist with male-to-female shamans. The Zulu of South Africa also initiate transgender shamans, calling them insangoma. In Ethiopia, the Amhara allow intermediate, mixed, or third gender expression, which appears to be more acceptable than gender assignment surgery. The Otero, to the north-east in the Sudan, follow the same blueprint when it comes assessing gender identity. Despite this long history across the continent, the colonization of much of Africa during the eighteenth and nineteenth centuries brought considerable religious repression, including suppression of any unusual sexual behavior, out of which many countries have only recently emerged.

[37] Behrens KG, A principled ethical approach to intersex pediatric surgeries, *BMC Medical Ethics*, 2020;21:108. doi:10.1086/s12910-020-00550-x.

Native Americans have often held intersex, androgynous people, feminine males and masculine females in high respect; such persons may be referred to as 'two-spirit' people or (more in the past) as 'berdache' when French explorers adapted the Persian word "bardaj", an intimate male friend. The term berdache had a clear homosexual connotation, but many focused on the reflection of their spirit, androgynous or transgender persons being seen as having both the spirit of a man of a woman; their gender status is different from both men and women. This allows a range of identities, from slightly effeminate males or masculine females to androgynous or transgender persons, to those who completely cross-dress and act as the other gender. Two-spirit people were respected not only because of religious attitudes, but also because of practical considerations, since they could do the work of both men and of women. Two-spirit persons assisted their siblings' children and took care of elderly relatives, and often served as adoptive parents for homeless children. The gender-conforming spouse of two-spirit people did not see themselves as 'homosexual' or as anything other than normal. As in Africa, homophobic European Christian influences diminished respect for same-sex love and for androgynous persons and two-spirit people were often forced to conform to standard gender roles. This is now itself in reverse, and a new respect for androgyny has started to re-emerge and the spiritual gifts of androgynous persons have become more recognized.

Within Judaism, early interpretations of the Genesis believed that Adam was androgynous but there is considerable confusion and ambiguity on the subject in both Hebrew and Christian bibles. With so much depending on certain words, after multiple translations, especially in relation to whose 'image' and whose 'likeness' Adam was made in, it is not surprising that there has been much uncertainty over the complex issues. Central to the discussion, which, for example, is contained within the Plato Symposium previously discussed, is the concept that when God created the first man he created him androgynous, which incidentally implies that God himself would have to be an androgyne since Adam was created in his likeness, but subsequent events, especially the creation of Eve from Adam's rib, focus on the physical differentiation of male and female from a single anatomical entity. It is best I leave the matter there, in view of the philosophical complexity and of the total confusion that arises from readings elsewhere in these religious texts, for example the story of Sodom and Gomorrah.

In modern-day Christianity, views are still highly polarized, reflecting the societies in which they are based. In 2019, the Vatican published a document on gender theory[38], ostensibly written as a guide for educators, but producing a clear rejection of the concept of transgender identity, with phrases such as '*gender binary is nothing more than a confused concept of freedom*,' where transgender impulses should be perceived as challenges to overcome.

At the end of 2018, the Church of England issued advice to members that recommended an adapted affirmation of baptism service to allow transgender Christians to celebrate their new identity. The guidance was rapidly criticized by many bishops who described it as "*theologically and pastorally questionable*", and which "*allowed themselves to be hijacked by these very small special interest groups*". It was noted that many parents and teachers were expressing concern about these new theories; they did not wish to cause harm to the tiny number of children afflicted by gender dysphoria but neither do they want to harm the potentially large numbers of children by imposing untried and untested ideas on young children. The conservatives believe gender is assigned by God and cannot be changed.

3.1.3.2.3 Transgender therapies today: Ethics, practices and difficulties

It is not surprising that, given the mythical origins of androgyny and the hugely variable manner in which different societies have treated the subject over centuries, public attitudes and, indeed, clinical acceptance, of available therapies are still unsettled, and often divisive. During the 1920s, several clinics in Europe

[38] Congregation for Catholic Education, "Male and female he created them" Towards a path of dialogue on the question of gender theory in education, Vatican City, 2019.

opened sexual science facilities, often based on the concept of transvestism and the need of cures for the 'mental affliction' of transgender patients. The second world war brought an end to much of the experimental sex change work. This was taken up seriously in the USA, with a major facility in Johns Hopkins University becoming a world-leader, but a report critical of the outcomes in 1979 caused that to be closed down and a bizarre format of medical tourism took over, with surgeries being performed in Casablanca and Tijuana. The main difficulties arise with the uncertainties over treating young people, especially with the use of puberty-blocking hormones, the implications for fertility and family development and the not-infrequent occurrence of regret and the search for revision, or reversal, methods[39].

3.1.4 Xenotransplantation

Xenotransplantation involves the transplantation of living cells, tissues, or organs from one species to another. In the context of this book, this term has come to be associated with the transplantation from a non-human animal into a human recipient. The term is also used when human body fluids, cells, tissues or organs have *ex vivo* contact with live non-human animal cells, tissues or organs.

According to Cooper *et al*[40], several cases of the use of animals (specifically non-human primates) for the procurement of organs for human transplants took place in the 1960s and subsequent decades, but several serious constraints were encountered, and the practice is still neither widely accepted, regulated or used clinically (in 2018 the first report of a successful transplant of a genetically-modified pig's heart to a baboon was released in Germany). These constraints embody ethical, scientific, and legal questions, principal of which are the risk of disease transmission from animals to the recipient and beyond, questions of human identity, and issues of animal welfare and abuse. It is convenient to deal with the scientific aspects first before the ethical / metaphysical aspects. The discussions will focus on the use of either pigs or non-human primates, and applications in major organ transplantation.

3.1.4.1 Infectious Disease Risk

Disease transmission from donor to recipient has always been a concern in organ transplantation. In clinical practice with deceased human donors, every effort is made, subject to the imposed time constraints, to assess bacterial and viral infectivity risk arising from the donor. Due attention must be paid to the fact that the recipient is going to be heavily immunosuppressed in order to minimize risk of organ rejection, so that they may be unduly compromised with respect to the risk of donor-transmitted disease.

Two factors may influence this infectious risk in relation to putative xenotransplanted organs. The first is that there is likely to be much less inherent immune protection in the recipient when exposed to a pathogen that may be common to the donor species but not found in humans. The second is concerned with subsequent human – to – human transmission. If in a normal donor-recipient transplant, some infectious agent is transmitted to the recipient, it is highly unlikely for that infectious agent to be transmitted to other humans because of natural immunity. With xenotransplantation, any virus that is transmitted, say, from a pig to a human, that host may have no natural immunity and, should that disease be transmitted to any other humans, they would have no immunity; it is easy to speculate how an epidemic, or indeed pandemic, could be established. I write this in December 2020 with the world in

[39] Bizic MR, Jeftovic M, Pusica S, *et al,* Gender dysphoria: Bioethical aspects of medical treatment, *BioMedical Research International,* 2018; ID 9652305. doi:10.1155/2018/9652305.
[40] Cooper DKC, Gaston R, Eckhoff D, *et al*, Xenotransplantation – the current status and prospects, *British Medical Bullein*, 2018;125:5-14. doi:10.1093/bmb/ldx043.

serious COVID-19 pandemic mode and the public are unlikely to accept additional pandemic risks for the sake of a minor increase in the availability of organ transplants.

Transmission of infections across species, and specifically from animals to humans, is generally encompassed by the term 'zoonosis', sometimes referred to as 'xenozoonosis'[41]. Attention has been focused on the correlation between swine and immunocompromised humans, which share some common pathogens. Specifically, although swine herpes viruses such as porcine cytomegalovirus and porcine lymphotropic herpes virus are mostly species specific and do not normally infect human cells, the porcine endogenous retrovirus (PERV) can infect some human cells since they have the necessary receptors. While such infectivity remains a possibility, the pre-clinical and clinical studies that have been performed have failed to demonstrate transmission of PERV to humans. This is important since the potential use of porcine islets in transplantation to diabetic humans represents a very attractive future option[42].

One possible way around this potential scenario could involve the use of genetically engineered pigs, which *de facto* allows modification of the donor in order to reduce risk. This relies on the deletion of expression of one or more of the three key pig antigens and /or the insertion of a human transgene that provides protection from human complement activity. Several genetic manipulations have been carried out in pigs that may overcome the physiological barriers to xenotransplantation and reduce transmission of potentially infectious microorganisms.

3.1.4.2 Metaphysical Aspects: Ethics and Spirituality

3.1.4.2.1 Animal welfare

I will deal with the issue of animal welfare first. It is clear that if animals, almost certainly pigs, will be used as an alternative source of organs for human transplantation, they will have to be kept under strictly controlled conditions; the most likely scenario is that they will be genetically modified and maintained under strict gnotobiotic protocols (i.e., with control of pathogenic microorganisms). The conditions of animal husbandry here almost certainly would be better than that provided for most farm animals used for food (or other product) supply; most relevant international organizations subscribe to the so-called five freedoms, which are freedom from hunger and thirst, freedom from discomfort, freedom from pain, injury or disease, freedom to express normal behavior and freedom from distress[43]. Even if these freedoms were rigorously applied, and indeed it would be completely in the interests of any commercial operation running such a regulated facility to do so, there cannot be any guarantee that the psychological and biological nature will not be upset in any way. We therefore have to accept that there will be some people who genuinely believe that it would be unethical to raise and 'harvest' pigs for this purpose, just as there are, now, very many people who object to using pigs for human food (even if a billion are used this way annually) or to the use of any animals in the testing and regulatory control of products that are discussed in this book.

3.1.4.2.2 Spirituality

It could be argued that there is little to discuss about the spiritual aspects of xenotransplantation; if an individual is naïve enough to believe that the heart is the seat of all emotions, so that if that person receives the heart of a pig, they now have the emotions of a pig and are themselves 'less than human', it is because of a fundamental lack of knowledge, especially about science. While it is my view, as a scientist,

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[41] Fishman JA, Infectious disease risks in xenotransplantation, *American Journal of Transplantation,* 2018;18:1857-64. doi:10.1111/ajt.14725.

[42] Ellis C and Korbutt GS, Justifying clinical trials for porcine islet xenotransplantation, *Xenotransplantation,* 2015;22:336-44. doi:10.1111/xen.12196.

[43] Rollin BE, Ethical and societal issues occasioned by xenotransplantation, *Animals,* 2020;10:1685. doi:10.3390/ani10091695.

that this may be substantially true, we would ourselves be naïve if we did not pay attention to the marked antipathy, on spiritual or faith-based grounds, of so many people to the concept of this use of animals for human benefit. At the simplest level, in Jewish and Muslim religions, the pig is regarded as an impure animal, which does restrict acceptance of this process.

From a faith-based perspective, Christians are taught in Genesis that "*God created the world and everything in it*' but also that '*humankind was created in the image of God*", which implies that humans have a relationship with God that differentiates them from all other creatures[44]. In fact, Genesis goes on to say that humans were intended to subdue the earth and to be the '*masters of the fish of the sea, the birds of heaven and all the living creatures that creep along the ground*'. While this potential dichotomy of humans being both a general consequence of the creation but also having a special role within it, is not necessarily a destabilizing concept to the vast majority of people under the vast majority of circumstances, it does have implications in this use of animal organs. Humans do not like to consider themselves as animals, in which case is it ethical for those same humans to consider it acceptable to use the organs from these lower species to save their own lives? Innate value of life and innate dignity are at the core of the argument. Any true acceptance of innate animal dignity implies an equality of human life and animal life and I doubt if society today would thrive on any such universal acceptance. It may be that faith beliefs, based on unscientific knowledge, and the norms of human behavior today, based on poor historical and philosophical knowledge, have to move towards each other.

We may sum up this position with two sentences from George Orwell's classic 1945 satire 'Animal Farm'[45];

"All animals are equal, but some animals are more equal than others".

"The creatures outside looked from pig to man, and from man to pig, and from pig to man again; but already it was impossible to say which was which".

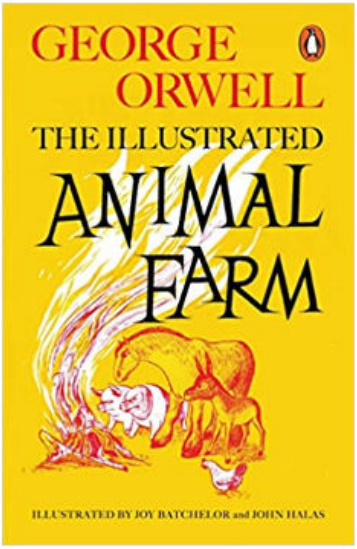

Figure 3.6. George Orwell's political satire "Animal Farm", 1945.

[44] Ebner K, Ostheimer J & Sautermeister J, The role of religious beliefs for the acceptance of xenotransplantation. Exploring dimensions of xenotransplantation in the field of hospital chaplaincy, *Xenotransplantation,* 2020;27:e12579. doi:10.1111/xen.12579.

[45] Orwell, George, Animal Farm, Secker and Warburg, London, 1945.

3.1.5 Clinical Trials

As I write this, towards the end of December 2020, arguments are raging across the world, focused on the USA, about the introduction of vaccines to deal with the COVID-19 pandemic. I will not anticipate the outcome of such arguments, but it is clear that a serious ethical issue has arisen with respect to the speed of release of several vaccines for public use, initially with so-called emergency use authorization. It normally takes many years to develop and test new vaccines, rather than the six months or so with some COVID-19 products. The questions naturally arise as to the scientific standards used to test for safety and efficacy, including the phases of clinical trials in humans. There has, of course, been an immense political dimension to this, particularly in the USA with an imminent election and the UK where Brexit talks had not been finalized, which included issues of cross-border trade and regulation of medicines. Central to the subject matter of this section are the ethical issues of performing clinical trials on new healthcare products. In the interest of full disclosure, I should mention that I am Chairman and Founding Director of a company in South Africa that, for 10 years now, has been developing new technologies for reconstructing the heart valves of children suffering from and dying of rheumatic heart disease; we would have commenced clinical trials this year if it hadn't been for the pandemic and the closure of many hospitals to non-Covid-19 elective surgery. I deal with the relevant scientific, clinical and epidemiological issues elsewhere in the book, but the decision processes involved with using unique, potentially lifesaving but otherwise untested implant technology in Africa's children encompasses many of the aspects that feature in this section.

I deal with this subject generically (i.e., covering the principles of clinical trial ethics in general) but with a final commentary on differences between products of medical technologies relevant to reconstructing the body and pharmaceuticals.

3.1.5.1 Standard-of-Care Versus Progress

The Belmont Report, published by the Department of Health, Education and Welfare of the United States Government, in 1979, represents the basic framework for the ethical principles underlying the protection of human subjects in medical research[46]. Central to the discussion here is the concept of the therapeutic obligation, which is the physician's duty to provide patients with what he / she believes is the best available treatment[47]; it is assumed that clinical interventions are designed solely to enhance the well-being of the individual patient and are considered to have a reasonable expectation of success. This is broadly aligned with the concept of 'standard-of-care', although this has legal overtones (which vary from one jurisdiction to another) and is related to the degree of care and skill which a provider applies to a patient, taking into account the available medical knowledge. All this implies that when a patient is attended to by a physician, they should expect careful and skillful treatment of their condition consistent with, but not beyond, the current professionally accepted methods.

The implication of this generally sensible position is that if the physician does not consider that he / she has adequate tools available to treat a particular patient or group of patients, an alternative approach may be used, in which case alternative ethical considerations should apply. This clinical scenario is sometimes referred to as 'experimental' or designated as 'research', there being a degree of cynicism attached to both

[46] The Belmont Report, US Government Department of Health, Education and Welfare, Pub (OS) 78-0013 and 78-0014, April 18th 1979.
[47] Merli D and Smith JA, Reconceiving the therapeutic obligation, Journal of Medicine and Philosophy, 2014;39(1):55-74. doi:10.1093/jmp/ht057.

terms. It has been strongly argued by Kowalski *et al*[48] that there should be no distinction between research and accepted therapy, concluding that such a separation '*fails along ontological, ethical and epistemological dimensions*'; I concur with that position.

The reality is that the practice of medicine has to evolve, usually slowly but sometimes rapidly, to take advantage of new scientific knowledge and societal positions, but ultimately it is the specific physician – patient relationship, based on ethical and legal principles, that is paramount in decisions about therapeutic procedures, and these should be controlled by accepted professional standards. There are boundaries that should not be crossed when considering experimental therapies but, although the nature of these boundaries may vary, the principles should not be different to those that apply to standard-of-care treatment; even if the '*primum non nocere* (first do no harm) principle is outdated in today's environment, the mandate to apply a risk – benefit evaluation in every situation is universal.

I had the privilege of meeting some of the pioneers of reconstructive and transplant medicine in the 1970s and it is clear that, even though there was no oversight by professional organizations and committees, the vast majority of these pioneers were very mindful of their ethical obligations. Many ground-breaking innovations may not have taken place in more restrictive environments; hip replacements, heart and kidney transplants and prosthetic heart valves were all used clinically before the introduction of oversight. In the USA, this involved the establishment of Institutional Review Boards (IRBs) in 1974, now governed by the latest codes, in 2018[49]. One of the major outcomes of the discussions to set up IRBs was the formulation of guidelines for the conduct of clinical trials.

3.1.5.2 The Need for Truth; Evidence-based Medicine

In 2020, truth and facts have become contentious issues, as so-called alternative facts and unequivocal lies have competed with them in public media, and especially social media, not just in the highly publicized domains of the USA, but around the globe. I will avoid that broad debate and focus on truth and, its converse, bias, in the reporting and discussion of medical progress. If I carried out a clinical study involving a variant on a medical device procedure, and did so without any institutional oversight, it would be entirely possible for me to deliberately misrepresent the results in order to influence acceptance of the new variant, which could possibly be named after me! Even without that formal oversight, it would be difficult to do this in a blatant, misleading manner, since it would be obvious to many well-informed participants in the study. However, 'bias' in interpreting clinical data may not be so easy to identify[50], bias being defied as '*a cause of systemic error*', '*a deviation in judgement*' or '*a deviation from the truth*'.

3.1.5.2.1 Truth, knowledge and power

Without getting too deep into the philosophy of truth, it is useful to reflect on Foucault's views on truth, knowledge, and power[51]. Foucault was a very influential twentieth century philosopher who presented hypotheses on the interaction between knowledge and power; power is everywhere, he contended, diffused in knowledge and 'regimes of truth', which are in constant flux and negotiation. Power is constituted through accepted forms of knowledge, scientific understanding, and truth, which is itself only produced by virtue of multiple forms of constraint. To Foucault, each society has its regime of truth, and

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[48] Kowalski CJ, Hutchinson RJ & Mrdjenovich AJ, The ethics of clinical care and the ethics of clinical research: Yin and Yang, *Journal of Medicine and Philosophy,* 2017;42(1):7-32. doi:10.1093/jmp/jhw032.

[49] Human Participant Protection Regulations, and Protection of Human Subjects, United States; 45 Code of Federal Regulations Part 46, 2018.

[50] Wieringa S, Engebretsen E, Heggen K, *et al*, Rethinking bias and truth in evidence-based health care, *Journal of Evaluation in Clinical Practice,* 2018;24:930-8. doi:10.1111/jep.13010.

[51] Foucault M. (Translated by Sheridan A.) Discipline and Punish: The Birth of a Prison. London, Penguin. 1991. ISBN 0679752552.

within this, the types of discourse which it accepts, and makes function, as true. This implies that each society defines the mechanisms that enable true and false statements to be distinguished and the means by which each is sanctioned.

With respect to the enhancement of knowledge about healthcare products and techniques, there are two main processes of acquiring data and several methods of promulgating the data and its interpretation. The first process involves scientific laboratory research without applications to humans, and the second is the evaluation of the techniques in actual patients. Data from the first type are usually published as scientific papers, conference reports or patent filings. Depending on how the clinical evaluation is carried out, results can also be published in papers and reports but also as part of regulatory submissions for marketing authorization.

Bias, or plain untruthful reporting, can occur in all these phases. The controls that should apply to regulated clinical trials probably reduce the negative effects of untruthfulness.

3.1.5.2.2 Truth and lies in scientific journals

As a former Editor-in-Chief of a major global journal in the medical technology sector (*Biomaterials*, 1996-2014), I witnessed an increase in 'unscientific conduct' and indeed 'scientific fraud' in recent years. Academically this was mostly associated with plagiarism, which, although being a serious offence, did not directly affect the truth of scientific discourse. On the other hand, image manipulation, that is the deliberate alteration of images with the intention to distort the data in order to enhance 'proof' of the author's hypotheses, became a profound problem[52]. I was pretty good at detecting plagiarism, and we had increasingly effective software to help us, but I had little experience at the detection of image manipulation. Today, a few years later, there is good software for that purpose (and, incidentally, software to assist in the original manipulation) but still, even with reputable journals in our sector, between 5 and 20% are found to have some degree of manipulation. Even without such intentional deception, many papers contain more subtle bias, for example including a conclusion and/or abstract section that refers to positive outcomes even when the data discussed in other sections make it clear that differences were not statistically significant. This problem is exacerbated by the laziness of many scientists who cite such erroneous conclusions in their own paper to support their own views but without reading the full papers.

The magnitude of the problem is difficult to assess but should not be underestimated. Deliberate falsification of experimental data takes place alongside the well-known phenomenon that the results of much experimental work cannot be reproduced, either in the author's own laboratory or elsewhere[53]. According to Flier[54] about 2% of scientists admit having personally fabricated or modified data at least once and said 14% of their colleagues had done the same. All of this is very concerning and points to the need for even more rigorous protocols for first uses of new devices and technique in man.

3.1.5.2.3 Assessment of the clinical performances of medical technologies

Before extensive, hopefully definitive, clinical trials are performed, it is sometimes necessary to carry out a type of pilot study, especially where there is little or no previous experience using the device with humans. Such studies are not usually analytical trials designed to test a hypothesis but focus on gathering data for use in optimizing the design. Some common objectives of pilot studies for medical devices are summarized below. Some are used to assess the safety of new products for which clinical experience is

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[52] Bucci EM, Automatic detection of image manipulations in the biomedical literature, *Cell Death & Disease,* 2018;9:400. doi:10.1038/s41419-018-0430-3.

[53] Loscalzo J, Experimental irreproducibility: Causes (mis)interpretations and consequences, *Circulation,* 2012;125(10):1211-4. doi:10.1161/CIRCULATIONAHA.112.098244.

[54] Flier JS, Irreproducibility of published bioscience research: Diagnosis, pathogenesis and therapy, *Molecular Metabolism,* 2017;6:2-9. doi:10.1016/j.molmet.2016.11.006.

minimal or nonexistent. These are usually 'open-label studies', performed without a control group, conducted at a single site with few subjects. From the perspective of a user, usually a health-care professional, the preliminary performance evaluation will include gathering data on such design features as ease of use, reliability, and control, and on the suitability of the instructions for use. A pilot study can address the effectiveness criteria for use in a pivotal clinical trial. These pilot studies are often referred to as 'First-in-Man' (FiM) clinical use; they have to be approved by the relevant IRB (or Ethics Committee in some countries), the oversight dimension being rather variable. Ethical standards should be very high, but this is not always apparent. It is often the case that a clinical team in Europe or North America, together with their commercial sponsors, will undertake FiM studies in South America or Asia, with the help of a local partner who obtains ethical approval. The opportunities for bias are obvious.

Some pilot studies, especially involving major innovations with few patients, are sometimes called observational studies. As described by Bernard *et al*[55], the use of such studies should remain exceptional, although definitions of what constitute an observational study vary considerably. Again, without the formal oversight constituted by a clinical trial there are opportunities for error and mistakes, the most egregious of which can constitute malpractice and criminal behavior. Currently one such case is progressing through the criminal courts of Sweden where a surgeon, working on a tissue-engineering approach to the replacement of diseased tracheas, during which series several patients died, has been charged with aggravated assault[56]. Since the process is still *sub judice* I will make no specific comment but merely point to the dangers of essentially unregulated clinical 'firsts'; the prosecuting authority stated "*it has become clear to me that the operations were carried out in conflict with science and proven experience, and were therefore not carried out based on any legal form of medical care or licensed research study*". In the interests of full disclosure, I knew the surgeon, Paolo Macchiarini, and had published some of his pre-clinical work in my journal *Biomaterials,* but never carried out any research with him.

A randomized controlled trial (RCT) is a study in which individuals are allocated at random to receive one of several clinical interventions, which include the new therapy and the control. The control may be a standard practice, a placebo, or no intervention at all. In an ideal world these trials use double blind methodology, where neither the patient nor the treating doctor know to which group they have been allocated; only those directing the study have this information.

Not all clinical trials are without problems and there can be no guarantee of conclusive outcomes, but they do represent the best procedures today. Some of the issues faced with clinical trials are covered in the following sections.

3.1.5.3 Respect and Informed Consent

I will discuss some significant differences between the practicalities of clinical trials with products for reconstruction and those for pharmacological interventions in a following section; there are some implications for informed consent within these differences here, but in this brief section I will mention the nature of informed consent from a generic perspective even if in practice they are more appropriate for pharmaceuticals.

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[55] Bernard A, Vaneau M, Fournel I, *et a*l, Methodological choices for the clinical development of medical devices, *Medical Devices: Evidence and Research,* 2014;7:325-34. doi:10.2147/MDER.S63869.

[56] Swedish Prosecution Authority, Solna District Court case number: B 10553–18, Prosecution of a Former Surgeon at Karolinska University Hospital, Published: 9/29/2020 9:43:14 AM.

It has been known from the inception of formal rules for clinical trials that there is an inherent conflict between randomized trials and the therapeutic obligation[57]. Medical professionals have a duty to promote the best interests of their patients within the constraints of the law and available resources[58]. On the other hand, research personnel (which include clinicians and non-clinicians) have the responsibility to advance scientific knowledge which ultimately will serve the interests of future patients. It could be argued that different ethical principles apply to these two groups, especially since the researchers do not implicitly aim to provide their participants with the best possible care, since doing so may not meet the goals of the research. My position is that the basic ethical principles do not change with these two groups, although the methods of complying with ethical standards may vary.

This position is based on the concept that it is not necessarily the medical benefit that is core to ethical standards, but the respect shown to the patients, and this is reflected by the practices of informed consent. It is the duty of all investigators to obtain informed consent from a patient, which embodies the requirement to respect persons and their own autonomous decisions. Informed consent is more than providing a patient with a document and asking them to sign it. Participants must understand and appreciate the information, and hard questions may arise, especially when where the science and technology may be complex and where there is insufficient knowledge about the risks involved. Equally the patient may either be inherently unable to understand what he / she is being told or may be too ill to provide sound judgement. The consequences of exploitation and paternalism are important here since information has to be provided in a neutral, unbiased way, but arrogant assumptions that the doctor knows best and advises the patient accordingly have to be avoided.

3.1.5.4 Cultural Diversity and National Exploitation

Some profound ethical challenges face the expansion of clinical trials into so-called low-to-middle income countries (LMICs) across the globe[59]. Although some would argue that conducting clinical trials in the poorest regions of the world is intrinsically immoral, that is not the case. Often, the local population have no recourse to what could be considered the standard of care in high income countries (HICs), so a clinical trial might be the only way in which a percentage of affected patients could receive any form of treatment; if the trial is successful, then large regions could potentially benefit. On the other hand, there is the temptation to take advantage of deprivation to impose high levels of risk on participants that would be unacceptable elsewhere. Multinational pharmaceutical companies are carrying out an increasing proportion of their clinical trials in LMICs. It is a fact that regulators such as the FDA, and international positions in general, for example the Declaration of Helsinki, have taken a more relaxed approach to the oversight of clinical trials on a global basis[60].

It is also necessary to consider where the most suitable patients are. For example, the development of heart valve technology for rheumatic heart disease patients which I referred to earlier can only be tested clinically in regions where rheumatic disease is endemic. There are essentially no cases of the disease in HICs, so we are planning to carrying out FiMs in South Africa and clinical trials elsewhere in sub-Saharan Africa, and possibly in other BRICS countries (Brazil, Russia, India and China).

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[57] Gifford F, The conflict between randomized clinical trials and the therapeutic obligation, *Journal of Medicine and Philosophy,* 1986;11(4):347-66. doi:10.1093/jmp/11.4.347.
[58] Jansen LA, Taking respect seriously: Clinical research and the demands of informed consent. *Journal of Medicine and Philosophy,* 2018;43:342-60. doi:10.1093/jmp/jhy006.
[59] Weigmann K, The ethics of global clinical trials, *EMBO (European Molecular Biology Organization) Reports*, 2015;16(5):566-70. doi:10.15252/embr.201540398.
[60] Cohen TL, Expendable commodities: The exploitation of human research subjects in the developing world, *International Journal of Applied Philosophy,* 2018;32(2):219-29. doi:10.5840/jap2019212112.

It has to be expected that there are cultural differences in various communities. As argued cogently by Chattapadhyay & De Vries[61], diverse cultures and moral traditions share a common world, but they have to be given serious consideration 'when Western bioethics travels abroad':

"*Can and should Western bioethical theories and methods be applied to Ayurveda, Acupuncture, Unani-tibb* [a holistic form of medicine *originating in India*]*, Navajo medicine or any other indigenous traditional system of medicine? How does ethics, as a branch of Western philosophy relate to dharma* [*concepts of universal truth within some religions such as Buddhism*] *or to Eastern philosophical systems and worldviews? Is mainstream Western secular bioethics sensitive to the moral aspirations and needs of citizens of non-Western societies? How does an individual-centered, rights-based bioethics resonate with the cultural ethos of traditional societies?*"

They argue that we must find common grounds of morality across different cultures, acknowledging and respecting cultural and moral diversity. Interestingly they finish their essay with the Hindu spiritual tradition of considering something as not '*wrong*' but on a *'lower plane of truth'*.

3.1.5.5 Payment for Participation

I raise this matter only briefly here; it is a very important issue in the clinical trials arena but is only marginally relevant to the technologies of reconstruction. Because the ability to recruit a suitable number of participants for clinical trials is a major challenge to sponsors, there has been a tendency in recent years to offer financial inducements to potential participants[62]. This is most commonly seen in phase I pharmaceutical trials. which essentially involve healthy volunteers to whom drugs are applied in order to test for safety. Ethical and regulatory orthodoxy here has implied that volunteers for such clinical trials are merely test subjects whose contribution is essentially benevolent or altruistic. However, once payment is formalized, these individuals *de facto* become part of the research infrastructure, with expectations of some of the benefits of employment. Moreover, payment may be seen as an inducement to take part in a process against better judgement, and questions arise as to how often such individuals should be exposed to new drugs. There are several interesting philosophical arguments to be considered here, but since it is difficult to perceive of any individual participating in a clinical trial of medical technology products in this way, I shall take the matter no further.

3.1.5.6 Differences Between Healthcare Products

In several product liability litigation cases about implantable medical devices in which I have been involved, the plaintiff's arguments usually include (often without any substantial evidence of harm) that the device was not properly tested, that the 'injured' plaintiff was treated as a guinea pig, and no clinical trials were performed. This position about clinical trials fails (usually intentionally) to recognize that clinical trials for products of medical technology are very different to those for pharmaceuticals. In the latter case, the clinical trials follow well recognized phases to test for safety and efficacy, when participants are administered the drug in question and followed for a specific time, initially measured in days or weeks, and later, pivotal trials, in more extensive periods. These procedures are, nearly always, carried out alongside controls. Wherever possible, they are randomized, double-blind, meaning that neither the participant not the treating clinician know who is getting the new drug and who is getting the control (usually a placebo). So far, so good, although it should be realized that clinical trials do not

[61] Chattopadhyay S and de Vries R, Respect for cultural diversity in bioethics is an ethical imperative, *Medicine Health Care and Philosophy*, 2013;16(4). doi:10.1007/s11019-02-9433-5.
[62] Malmqvist E, "Paid to endure"; Paid research participation, passivity and the Goods of Work, *American Journal of Bioethics*, 2019;19)9):11-20. doi:10.1080/15265161.2019.1630498.

always predict the outcomes when the drug is fully marketed, sometimes resulting in product withdrawals and then litigation.

It is easy to see that this scenario is very difficult to follow when a medical device or tissue-engineering product needs evaluation. Let us take hip joint replacements or prosthetic heart valves as examples. We already have some good, effective, products on the market and new devices are introduced in attempts to improve an already well-accepted concept or to make products available to a different cohort of patients, usually younger people, possibly with co-morbidities. The first point to make is that any such trials with these products cannot be double-blind since the surgeon has to know what he is doing. It is usually very difficult to offer a directly comparable control, and, in most cases the concept of a placebo (i.e., do nothing) is not feasible. Secondly, since these devices usually last a long time, measured in decades, how long should a trial last and what should be the end-point? To carry out a long-term clinical trial on most implantable medical devices is essentially impractical, especially as even newer products will be introduced (probably by competitor manufacturers) long before the results are known and evaluated.

With new products that have incremental changes compared to existing products, it is possible to carry out short term comparative studies, largely designed to evaluate any significant early safety issues. With most situations, however, especially when radically new designs and concept are involved (for example, with tissue-engineered organs), the normal practice is to use, under strict IRB control, the First-in-Man approach mentioned earlier, often case by case, with substantial review at many time points. Once significant evidence of safety and a reasonable chance of efficacy has been obtained, the sponsor can plan a pivotal, multicenter trial, with appropriate controls if possible. The outcomes of such studies, which of course are enormously expensive, will then inform regulators and insurers who have decisions to make about widespread use.

It is normal practice that clinical trials are registered at the outset (through clinicaltrials.gov). Major, respected, journals, will not allow publication of outcomes unless the trials were registered in this way, i.e., this cannot be done retrospectively.

3.1.6 Registries

In various sections of this book, the ability to assess the performance of devices and technologies used in reconstructive surgery is discussed and, as seen in the discussion of clinical trials, a number of ethical issues arise, especially concerning patient privacy and informed consent. For many decades, proposals have been made, and considered, for the establishment of centralized 'registries' of medical devices which could provide valuable information of device performance in the broad population in whom devices are used. In the USA, the Agency for Healthcare Research and Quality has considered this matter and published extensively on the subject[63] and the Pew Charitable Trust have published their recommendations[64]. The principles are clear and should be welcomed, provided attention is paid to the rights of those patients whose data is included in registries. In different countries, there are legal frameworks that govern the use of data from patients, including the Health Insurance Portability and Accountability Act (HIPPA) and the Federal Policy for the protection of Human Subjects, the so-called Common Rule that has already been mentioned; the Pew Report cited above indicates that there is widespread concern among physicians that submission of data to a registry violates HIPPA.

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[63] Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/ registries-guide-3.cfm.

[64] The Pew Charitable Trusts, Medical Device Registries; Recommendations for advancing public health and safety, 2014.

Kramer and Parasidis have put the use of compulsory medical device registries into the perspectives of device regulation, device performance reporting and patient safety[65]. Registries have been introduced following a series of high-profile 'failures' of certain products where there has been a clamor from the public and politicians for better levels of safety. As I discuss in detail elsewhere in this book, failures do not necessarily imply that a device has failed by some recognizable mechanism, for example mechanical failure or adverse tissue response, but rather that a product has failed to provide satisfaction to a number of individuals. In order to provide a better chance of success, it is necessary to identify the extent of the problem and the characteristics of performance issues. Ideally, as much information as possible should be obtained for each case of failure to achieve satisfaction so that remedial actions could be taken, including minor clinical interventions to the affected patients or removal of the product from clinical use. The obvious problem here is that the collection of such data is likely to contravene the ethical requirements of patient confidentiality. It could be argued that full scale clinical trials should be able to reveal potential problems, but these are rarely performed on sufficiently large numbers of patients to make any statistically valid conclusions. In addition, most regulatory bodies require that manufactures carry out post-market surveillance procedures, but these usually have limited value since the level of detail recorded may be insufficient and since reporting efforts are so variable in quality.

Centralized registries, in which sufficient and adequate data is obtained from clinics for certain types of device, using a mandatory process and oversight by an independent body, appears to offer a good solution. There are many reservations about how widespread these should be (geographical locations, types of device, nature of data stored and analyzed etc.) and there are clear implications with respect to costs and cost-benefits, especially with some low-risk devices.

Registries that are not mandatory may have limited use, especially as the outcomes of voluntary schemes are likely to be biased, with contributions to the bias coming from both patients and clinicians. As mentioned by Kramer and Parasidis, two major registries for high-risk cardiovascular devices (for implantable cardioverter defibrillators and transcatheter heart valves) during the last two decades have provided the basis for discussion of ethical issues since patient enrollment was obligatory (as a condition of reimbursement) but informed consent was not required and there was no opt-out possibility. These authors point out that consent protocols for compulsory registries would promote respect and build public respect for health data analytics and would require investigators themselves to know, and present with clarity, the registry goals, responsibility for its stewardship and provide avenues for patients to engage with professionals about the data, including their own data.

Capozzi and Rhodes have discussed some serious ethical implications with orthopedic joint registries[66]. The background for their concerns was stated to be that anything that can be used for good purposes can also be used in ways that may cause harm; it is important to know whether the data are being analyzed by an informed, competent and unbiased team. A majority view seems to be that, when used for high-risk innovative products, registries should be mandatory since the ability of physicians or healthcare facilities to avoid inclusion would inevitably lead to bias and distortion; some physicians would prefer not to be included since this could lead to poor comparisons with their peers or promote litigation by affected patients. Some courts have not found the value of registry information sufficiently important to justify interference with an individual practitioner's liberty to conceal information about their private practice outcomes. It is also noted that the need for informed consent and / or institutional review board approval may depend on the structure of the registry; if it is set up as an operation for public health or quality improvement, informed consent and approval is unlikely to be required, but this is not the case if it is

[65] Kramer DB and Parasidis E, Informed consent and compulsory medical device registries: ethics and opportunities, *Journal of Medical Ethics*, 2021;0:1-4. Doi:10.1136/medethics-2020-107031.
[66] Capozzi JD and Rhodes R, Examining the ethical implications of an orthopedic joint registry, *Journal of Bone and Joint Surgery*, 2010;92A:1330-3. doi:10.2016/JBJS.1.01410.

considered to have research objectives. With respect to informed consent, considerations of either 'opting-in' or opting-out' have produced significant disagreements, the former being the most popular position[67].

3.1.7 Medical Tourism

A 2014 Lancet Commission on Culture and Health[68] noted that planned and unplanned migrations, diverse social practices and emerging disease vectors are transforming how health and wellbeing are understood and negotiated. The report goes on to claim that all people have systems of values that are unexamined, and which are often diffuse and taken for granted, but which are dynamic and changing. It is worth considering their major assumption: "*In view of the fragility of so many systems of care around the world, and the wastefulness of so much healthcare spending, a line can no longer be drawn between biomedical care and systems of value that define our understanding of human wellbeing. Where economic limitations dictate what is feasible, socioeconomic status produces its own cultures of security and insecurity that cut across nationality, ethnic background, gender orientation, age and political persuasion*".

This implies that global healthcare should be moving towards a common goal, which is associated with financial and socioeconomic status. However aspirational this may be, we are a long way from that goal. Inequalities abound, which is why individuals who suffer from inequality on either count, often pursue their individual healthcare options by whatever means are available, which is the generic principle behind medical tourism. The reality, of course, is that the tourism focuses on the relatively poor individuals of high-resource areas who travel to generically low or mid-resource areas, where they can better afford medical care in commercially-driven facilities set up specifically for that purpose.

Figure 3.7. Medical tourism promotion.

[67] Bredenoord AL, Giesbertz NAA and van Delden JJM, Consent for medical device registries; Commentary on Schofield on the role of consent and individual autonomy in the PIP breast implant scandal, *Public Health Ethic*s, 2013;6:226-9. Doi:10.1093/phe/pht021.
[68] Napier AD, Ancarno C, Butler B, *et al,* Culture and health, *The Lancet*, 2014;384:1607-39. doi:10.1016/S0140-6736(14)61603-2.

That medical tourism is a rapidly expanding global phenomenon is not in doubt, nor are the ethical concerns that have arisen with this industry[69]. Medical and surgical procedures that are commonly associated with this activity include cosmetic plastic surgery, bariatric surgery for weight loss, orthopedic joint replacements and fertility treatments. Treatment costs are usually between 10 and 30% of those in the USA, and major centers are found in India, Thailand, Malaysia and Mexico. General criticisms and concerns involve exaggerated claims, lack of regulation, poor outcomes (including infections) and costs of remedial clinical work when patients return home. There are serious concerns about the widely used practice of vacation-based opportunities, where the total procedure costs include air travel and 'vacations' before or after the operation[70].

The major ethical issues surrounding medical tourism refer to organ transplantation, stem cell therapies, infectious diseases and funding.

Many intergovernmental organizations have addressed the need to prevent harmful practices related to organ procurement and transplantation, but many argue that more should be done[71]. While the purchase of organs from destitute persons and the removal or organs without valid consent have generally been banned by bodies such as the WHO, and individual countries have been incorporating such bans into national law, such practices clearly continue in several regions, and there are strong arguments in favor of so-called extraterritorial jurisdiction, where one country's laws extend to their subjects who attempt to travel overseas as 'transplant tourists'. To eliminate the global black market in organs is very challenging when individuals can travel from countries with strict law enforcement to those where the laws are poorly enforced or are loophole riddled.

Stem cell tourism has surfaced in many clinical areas, although a focus on incurable neurological diseases is particularly concerning[72]. The role of the internet and the acute anxiety of individuals who see no hope of getting better are central issues. This stem cell tourism is considered as an internet-based industry in which stem cell 'therapies' are advertised to patients as a 'cure' for their incurable disease. These procedures, usually but not universally being provided overseas, are, in the vast majority of cases, completely unproven, and are directed at those who are the most vulnerable, such as those with multiple sclerosis or amyotrophic lateral sclerosis (ALS) who are so desperate that they will ignore the lack of scientific or clinical evidence. The media, both mainstream but especially social, are rife with anecdotal stories and highly professionally made advertisements which wrongly attract the susceptible person.

One notable aspect of medical tourism (a topic that aligns with the section that follows this) is the growth of such tourism in Islamic countries[73]. There is a significant temptation in some of these countries to organize, at state level, medical facilities that can attract overseas visitors, with much needed international revenue; Malaysia is a good example. In such countries, this medical tourism has been interpreted as Islamic pilgrimages, which appears to be ethically acceptable, overseas participants being able to follow all religious customs and procedures. This has been extended to provide separate services for the different branches of Islam.

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[69] Foley BM, Haglin JM, Tanzer JR, *et al,* Patient care without borders: a systematic review of medical and surgical tourism, *Journal of Travel Medicine,* 2019;1-11. doi:10.1093/jtm/taz049.

[70] Iorio MI, Verma K, Ashktorab S *et al*, Medical tourism in plastic surgery: ethical guidelines and practice standards for perioperative care, *Aesthetic Plastic Surgery*, 2014;38:602-7. doi:10.1007/s00266-014-0322-6.

[71] Marttin DE, van Assche K, Dominguez-Gil B *et al*, Prevention of transnational transplant-related crimes – What more can be done, *Transplantation,* 2016;100:1176-84. doi:10.1097/TP0000000000001001.

[72] Bowman M, Racke M, Kissel J *et al,* Responsibilities of health care professionals in counseling and educating patients with incurable neurological diseases regarding 'stem cell tourism': Caveat Emptor. *Journal of the American Medical Association, Neurology*, 2015;72(11):1342-5. doi:10.1001/jamaneurol.2015.1891.

[73] Kamassi A, Manaf NHA and Omar A, The need for international Islamic standards for medical tourism providers: a Malaysian experience*, Journal of Islamic Marketin*g, 2021;12(1):113-23. Doi:10.1108/JIMA.03.2019.0051.

3.2 RELIGIONS AND FAITHS

It is impossible to discuss the ways in which external factors impact on our quality of life without reference to religions, faiths, and indeed rituals and beliefs. It will become obvious that I am neither a theologian nor a historian, but merely a lifelong, hopefully unbiased observer of events.

(To be completed, Q1, 2024)

3.3 COMMERCIALIZATION AND COMMODIFICATION OF THE HUMAN BODY

The simple question 'who owns my body?' does not have a simple answer; indeed, this is a prime example of the ethical issues that have no right answers. This is partly due to the ambiguity of the concept of ownership with respect to an individual person, and whether ownership changes from the living person to the deceased. Implications of the ownership question are seen in the context of the transfer of tissues and organs from both living and deceased bodies to recipients of homograft transplantation procedures and the use of patient derived tissues and cells for their use in commercial products, including such use in the absence of consent or even knowledge of that patient. The technical aspects of the uses of these homograft products and patient-derived entities will be discussed in relevant parts of Chapter 5; here we discuss some of the more important generic issues, with due attention to practices under different religious and jurisprudence scenarios.

3.3.1 Who Owns My Body?

I deal with ownership of the human body by reference, first, to philosophical aspects, then the non-legal positions taken within certain religions and organizations, and finally the current legal positions within some jurisdictions.

3.3.1.1 Philosophical Concepts

A major essay with the title given to this section was published in 1996 by Harris[74]. I shall take a short-cut with the discussion of his position by going straight to the conclusion: "*Invocations of self-ownership, as rhetorical or literary devices for emphasizing the bodily-use freedom principle, are, unobjectionable (if not taken too literally). But for all purposes connected with arguments about the just distribution of resources, nobody owns my body, not even me*". The arguments presented in the essay appear to be sound, albeit complex if one is unused to the terminology, and I find it difficult to produce any better argument or conclusion.

There have been, of course, many proponents of alternative scenarios; most would agree that there are only three possibilities, either you own your own body, someone or something else owns it, or nobody owns it. The second of these is largely equated with slavery and there are few who would now argue that slavery was or could be morally acceptable. The cessation of slavery has, possibly, been reflected most significantly by the hymn / poem "Amazing Grace", written by John Newton, a slave trader based in

[74] Harris JW, Who owns my body, *Oxford Journal Legal Studies*, 1996;16(1):55-84. doi:10/ojls/16.1.55.

Liverpool, who after coming very close to death in a storm off the coast of Ireland was converted to Christianity and worked tirelessly alongside Lord Wilberforce to bring slavery to an end, at least as far as the UK was concerned[75]:

> *Amazing Grace, How sweet the sound*
> *That saved a wretch like me*
> *I once was lost, but now am found*
> *T'was blind but now I see*

The argument does not quite stop there, however, for many religious groups have, either in the past or even today, determined that in marriage, the male 'owns' the body of the female. Some of the considerations here are discussed below in the context of the influence of religion on ownership.

On a pragmatic level, wife-selling was carried out in England, especially before the 1857 Matrimonial Causes Act was passed, since divorce was essentially impossible for most people and the selling of the wife by the husband was, if not common, regularly undertaken, long after the ban on slavery[76]; this practice was elegantly described by Hardy in the fictional 'The Mayor of Casterbridge'[77]. The considerations that applied to this sale, expressed below in abridged form, are of interest:

> *"I'll sell her for five guineas to any man that will pay me the money and treat her well, and he shall have her for ever and never hear aught o' me. Susan, you agree?"*
> *She bowed her head with absolute indifference.*
> *"Five guineas", said the auctioneer. "Do anybody give it?"*
> *"Yes" said a loud voice from the corner. The sailor unfolded five crisp pieces of paper, and threw them down on the table cloth. The sight of real money had a great effect on the spectators'*
> *"Before you go further, Michael, listen to me. If you touch that money, I and this girl go with that man"*
> *"I take the money, the sailor takes you. That's plain enough. It has been done elsewhere, and why not here"*
> *"Tis on the understanding that the young woman is willing", said the sailor blandly, "I wouldn't hurt her feelings for the world"*
> *"She is willing, provided she can have the child…very well, she shall have the child and the bargain's complete".*

Many of the arguments of ownership of a person's body are enshrined within the concepts of "self-ownership". Thrasher, in a recent extensive essay on this subject[78], strongly argues for the principle that we 'own our bodies':

> *"Self-ownership is a crucial moral and political concept that can earn its keep if we understand it not as a type of property right in the self, but rather as a set of territorial rights one has over one's body. This territorial conception of self-ownership avoids the traditional arguments raised against the property conception of self-ownership….accepting this conception of self-ownership, I*

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[75] Newton, J *Thoughts Upon the African Slave Trade*, Samuel Whiting and Co., London. 1811; Martin, B, *John Newton: A Biography*, William Heineman, Ltd., London. 1950
[76] Thompson EP, Sales of wives; Customs in Common, 1991, Merlin Press, London. ISBN 0-14-012556-6.
[77] Thomas Hardy, The Mayor of Casterbridge, 1886; see 2002 Modern Library Paperback Edition, Random House, New York.
[78] Thrasher J, Self-ownership as personal sovereignty, Social Philosophy and Policy, July 10th 2018; https://ssm.com/abstract=3246469.

argue, has considerable moral and political benefits without taking on the costs associated with other forms of self-ownership".

Figure 3.8. *Selling a Wife* (1812–14), by Thomas Rowlandson.

Thrasher notes that the concept of self-ownership has fallen out of favor among most moral theorists, being abandoned to libertarians who prioritize ownership as one associated with pure property rights over the freedom that ownership brings. He suggests that there are three variants of the concept of self-ownership, that is the property conception, the autonomy conception and the sovereignty conception. However, ownership as a simple concept of property does not seem to fit well with much current thinking and many prefer to think of self-ownership as the protection of individual autonomy, that is the liberties to make decisions and engage in certain actions. Again, not quite so simple; property self-ownership is a threshold concept, which you either have or do not have. Autonomy is scalar concept as you can be more or less autonomous. Thrasher cites the examples of addicts and severely mentally disabled individuals who may not be very autonomous but should not lose their basic rights, implied within property ownership, because they have reduced autonomy.

Thrasher prefers what he describes as sovereignty ownership which, as distinct from property or autonomy, delineates a sphere of authority that individual's uniquely have with regards to their bodies and actions. Put simply, this concept denotes the position where an individual has supreme territorial jurisdiction over their body and the right to make decisions concerning their actions; within the body, only the individual may decide how the body is used. An important point is that this right does not mean that the individual always has effective control of their body; biologically and medically this is impossible. The point is that this concept limits who else has the authority to interfere within one's body.

One final thought (or collection of thoughts) on this subject concerns the question of whether the body is divisible with respect to ownership. I will cover some practical aspects of this in sections on organ and tissue transplantation, including transplantation from living donors (e.g., concerning kidneys) and with massively visible procedures such as face transplants. At a practical level, society must consider what is generally referred to as 'human waste', usually but not always matter that is excreted from the human body. In the general context we have no interest in that matter in this book, but since stem cells can be derived from urine (see Chapter 5) we may have to be careful here with that distinction. There are some

borderline issues. We do not normally consider hair in the context of ownership and indeed the disposal of hair that is cut of in salons is considered either as a nuisance waste or a resource[79]. However, human hair is considered a prime resource for the derivation of keratin-based biomaterials[80] and cosmetic products, and some types of hair are better than others.

Since I will be discussing in considerable detail the uses of materials / components / devices / transplants etc. in the reconstruction of our bodies, I should also mention the ethical, economical, and transactional aspects of the ownership of reconstructed parts. I remember a long time ago, when I had joint appointments in dental and medical schools in a UK University, watching a young dentist being escorted off the premises by police and being charged with the theft of gold retrieved from extracted inlay-adorned teeth. Most people who are treated with implanted devices die with them in place and ownership is never even considered. However, in some parts of the world, if patients with implanted pacemakers or defibrillators die at a time much earlier than the expected lifespan of the device, those devices can be re-sterilized and re-used. It has been argued that this practice is enormously beneficial for patients in LMICs, especially in Asia[81]. A major initiative at the University of Michigan in the USA (PMHYH, Project My Heart Your Heart) has shown that the two significant practical concerns about reuse, infection and malfunction, are not serious issues in most situations in these countries as this practice is not associated with higher rates of infection or mortality[82]. Principles of ethics and legal ownership co-mingle here. There is no clear internationally agreed view on who owns an implanted device. There has been mush discussion about ownership in the context of retrieval analysis of implants, probably with the consensus leaning towards ownership by the patient[83]. Other possibilities are the clinical facility in which the device was implanted, the implanting surgeon(s)[84] and the organization that paid for the device. Glister and Glister argue that ownership depends on whether the implant is fully incorporated, and therefore indivisible from, the body[85]. They argue that if it is not (as with a pacemaker), then on removal, a device is owned by the same person who owned it when it was first implanted; since they agree that this could be the patient, their estate, the insurer or the hospital, this does not get us very far. If it does become incorporated (or 'accede to the host body' in their language), then it ceases to exist as an independent object and the body-implant complex cannot be the subject of property rights. This conundrum exemplifies the difficulties that are faced in this situation.

Returning to the pacemaker issue, the ethical questions are broader than that of ownership. It is necessary to consider the individual and the collective aspect, and legal frameworks should be adjusted to facilitate the 'better good'. There is a powerful argument that determines that is for the common good that pacemakers explanted from deceased individuals should be refurbished (confining the concept here to the encapsulated microelectronics and battery but excluding the leads that carry current to heart tissue) and fitted to a patient in urgent need, rather than discarded. Patients in the category of urgent need are usually

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[79] Gupta A, Human air "waste' and its utilization: Gaps and possibilities, *Journal of Waste Management* 2014;ID 498018. doi:10.1155/2014/498018.

[80] Rouse JG and Van Dyke ME, A review of keratin-based biomaterials for biomedical applications, *Materials* 2010;3:999-1014. doi:10.3390/ma3020999.

[81] Selvaraj RJ, Sakthivel R, Satheesh S, *et al.,* Reuse of pacemakers, defibrillators and cardia resynchronization devices, *Heart Asia* 2017;9(1):30-33, doi: 10.1136/heartasia-2016-010828.

[82] Runge MW, Barman TS, Davis S, *et al*., Pacemaker recycling: A notion whose time has come. *World Journal of Cardiology* 2017;9(4):296-303. doi: 10.4330/wjc.v9.14.296.

[83] Mihalko WM, Retrieval studies in orthopaedic surgery: Editorial comment, learning every implant's story, *Clinical Orthopedics and Related Research* 2012;470(7):1803-4, doi: 10.1007/s11999-012-2307-6.

[84] Steinmann JC, Edwards C, Eickmann T, *et al.,* Surgeon ownership in medical device distribution: does it actually reduce healthcare costs? *Expert Reviews on Pharmacoeconomics Outcomes Research,* 2015;15(6):985-91. doi: 10.1586/14737167.2015.1067140.

[85] Glister J and Glister T, Property in recyclable artificial implants, *Journal of Law and Medicine* 2013;21(2):357-63, Pubmed ID 24597385.

those in LMICs where resources for the purchase of new pacemakers is limited. Apart from the technical risks mentioned earlier, there is the potential for causing more harm than good here if the patient is unable to access medical facilities for follow-up, which may be the case in those countries. Furthermore, international agencies have expressed concern about the optics of using '*discarded devices from high-income countries in poor disadvantaged patients in other parts of the world*'. Given goodwill, this does seem to be a soluble problem; whosoever is vested with the ownership of a device that is potentially reusable should be required to attest that such ownership would be transferred, without cost, to a regulated agency that was responsible for the humanitarian reuse of the device.

Another example of the divisible nature of the body, which is potentially of more importance generically, but of less relevance to the subject matter of this book, is saliva. Therapies for salivary gland dysfunction will be mentioned later, but it is the use of freely-donated saliva that has to be mentioned. It has become clear that saliva is an excellent source of DNA for genetic research and sequencing[86]. Vast numbers of individuals, world-wide, voluntarily provide samples of their saliva to commercial companies for purposes of providing an analysis of risks of genetic diseases and/or obtaining data on their ancestry. So far, so good; the tests are usually relatively inexpensive and potentially provide information to people who believe themselves to be susceptible to certain diseases or wish to know more about where they came from. Most of the companies involved are highly ethical and analyses are performed with appropriate privacy; importantly, the data is often entered anonymously into large databases, which is very valuable for genetic research, especially with respect to relatively rare diseases that cannot be investigated with individual sets of data unless they are pooled.

Of relevance to the discussion here is the ownership of DNA data. Not all commercial operations operate anonymously, sharing data only with explicit consent. Especially, some online websites permit individuals to search for relatives by providing their own genetic information. This is a recent phenomenon, and there are very few authoritative sources that deal with this; most discussion is confined to blogs and newspaper / magazine articles. The problem, however, is clear; if I find out that I have a susceptibility to a specific genetic disease, which by definition means that some relatives (whom I may not know) may also be susceptible, do I believe that I own my saliva, and own my genetic information, and have the right to alert those unknown relatives about this, including those who would rather not know.

I will summarize my thoughts on these matters shortly with respect to reconstruction of our bodies, but I have to say here that the above example, which is largely based on the power of the internet and social media, demonstrates the two sides of the phenomenal technological advances of the last few years, where our connectivity with everything outside our own bodies and minds, can be both of extreme advantage and danger.

3.3.1.2 Ownership Concepts within Religions and Cultures

Consistent with the lack of unanimity within philosophers about ownership of the human body, there is a variety of positions taken by religious leaders and pronounced in their writings. This is only to be expected, of course, but on close analysis, although the details may be different, there is some convergence about the main message, which is rather similar to that of the sovereignty concept discussed earlier.

Consider the Catholic Church, for example:

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[86] Goode MR, Cheong SY, Ning L, *et al.*, Collection and extraction of saliva DNA for next generation sequencing, *Journal of Visualized Experiments,* 2014;90:51697. doi:10.3791/51697.

> *Fundamental to Catholic bioethics is a belief in the sanctity of life: the value of a human life, as a creation of God and a gift in trust, is beyond human evaluation and authority. God maintains dominion over us. In this view we are stewards, not owners, of our own bodies and are accountable to God for the life that has been given to us*[87].

Most variants of Christianity share this view, and frequently cite the writings of St Paul in the bible, who uses the metaphor of the 'temple' to represent the human body:

> *"Your body, you know, is the temple of the Holy Spirit, who is in you since you receive him from God. You are not your own property*[88].

The Islamic perspective of ownership has been summarized by Aramesh as follows;

> *According to the Islamic view, the body, like the soul, is a gift from God; therefore a human being does not possess absolute ownership of his or her body. But the ownership of human beings on their bodies can be described as a kind of stewardship. Accordingly, any kind of dissection or mutilation of the corpse is forbidden, even with the informed consent of the dead or his / her relative. The exception of this principle is when such procedures are for saving lives of other people*[89].

Eisenberg, who has written extensively the Judaism view of the sanctity of the human body and Jewish medical ethics in general[90] expresses the situation as follows:

> *Judaism retains a markedly paternalistic view of medicine. The Torah states that the human body was created Bi'tzelem Elokim, in the image of God, and is the property of the Creator. Man is given custodial rights to his body and has no more right to destroy or harm his body than the superintendent has to ransack the building he is hired to maintain.*

In the *Samyutta Nikaya*, the Buddha says, "*This body is not mine or anyone else's. It has arisen due to past causes and conditions*" [91]. Death for the 20 million members of the Sikh religion is an essential path in the journey of life and is followed by rebirth through transmigration, the passage of the soul of a human being or animal after death into a new body of the same or a different species, without any reference, as far as I can see, to ownership of the body through this transmigration. Similarly, it is difficult to discern the concept of ownership within the writings on the Hinduism' perspective of the human body; there are many different facets of symbolism, with considerations of what is the body. The major concept is that the body is part of nature, indeed the representation of the universe itself, which clearly implies that self-ownership, as opposed to self-preservation, is not a consideration.

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[87] Markwell HJ and Brown BF, Bioethics for clinicians: Catholic bioethics, *Canadian Medical Association Journa*l, 2001;165 (2) :189-92.
[88] 1 Corinthians 6:19,20.
[89] Aramesh K, The ownership of the human body: An Islamic perspective, *Journal of Medical Ethics and History of Medicine*, 2009;2:4.
[90] Eisenberg D, Contemporary Issues in Medical Ethics from a Traditional Jewish Perspective: Essays Articles & Letters, Maimonides: Health in the Jewish World, Vol. 4, No. 2 (Spring 1998), 3.
[91] The Connected Discourses of the Buddha, A New Translation of the Samyutta Nikaya, Translated by Bhikkhu Bodhi, Wisdom Publications, Sommerville MA, USA, 2000.

3.3.1.3 Legal Considerations of Ownership

It is impossible to define a common legal system across the world where there are clear precedents and laws that cover the ownership of the body. Different nations have different sociological environments within which principles of jurisprudence are established and translated into laws that govern human behavior. Some systems rely heavily on common law, others on civil law and others on religious law. However, for present purposes, the pattern of discussion, the creation of laws, and arguments about the laws, are relatively consistent; end-points, especially those which result in divided opinions within Supreme Courts (or their equivalent), which demonstrate the general truth about the uncertainty of ethical issues that I have mentioned above

I shall start with the situation in the USA; in fact, most of the discussion is US-centric since that country is more advanced in the development of statutes that determine positions on complex issues, but yet is more divided on both the value and authority associated with the laws that are so enacted.

The discussions here do not uniquely address the human body in relation to reconstruction but covers both generic and specific issues that relate to what medical professionals, their institutions and related commercial entities, can do with tissues derived from human subjects. This will, *inter alia,* covers matters such as informed consent (or usually the lack of consent) and the distribution of income and profits following the commercialization of tissues. Two major cases dominate the landscape, those of so-called HeLa cells and the Moore v Regents of the University of California case.

3.3.1.3.1 HeLa Cells

Figure 3.9. Henrietta Lacks.

Many books and papers have been published on this landmark case; I specifically refer to the book by Rebecca Skloot[92] and the review of ethical and policy issues arising from the case published in 2016 by Beskow[93]. Briefly, a 30-year-old African-American woman, Henrietta Lacks, living in Baltimore, Maryland, USA, was diagnosed with an aggressive form of cervical cancer in 1951 at Johns Hopkins Hospital. Parts of the tissue samples taken from the patient were used for research purposes in a hospital

[92] Skloot R, *The Immortal Life of Henrietta Lack*s, Grown Publishing Group, New York, 2010. ISBN 978400052189.
[93] Beskow LM, Lessons from HeLA cells; The Ethics and policy of biospecimens, *Annual Reviews 0f Genomics and Human Genetics* 2016;17:395-417. doi:10.1146/annurevgenom-083115-022536.

laboratory. It was common at that time, and considered neither unethical or illegal, for tissues taken from patients that was in excess of that required for diagnosis to be used in such a manner, without the consent or knowledge of the patient or any relatives. What was unusual here was that the cells of the cancerous tissue were capable of survival and indefinite division in culture, a phenomenon hitherto unseen in such tissues. This information spread rapidly in the research community, and cell samples were distributed widely and freely within this community. The cells were labeled as 'HeLa', a name derived from Henrietta Lacks. The family of Henrietta received no financial benefits; she died quite quickly, and the family lived in poverty.

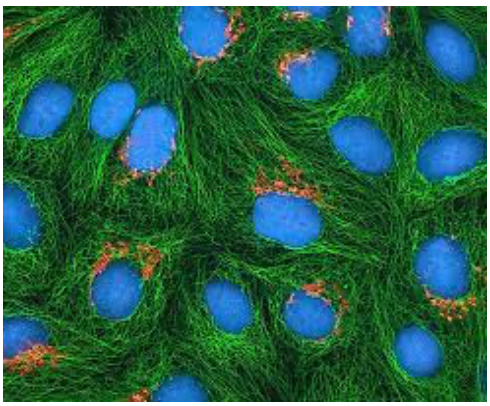

Figure 3.10. Fluorescence image of cultured HeLa cells with a fluorescent protein targeted to the Golgi apparatus (orange), microtubules (green) and counterstained for DNA (cyan). National Institutes for Health, USA.

The HeLa cells have been used world-wide for ground-breaking research, not only related to cancer but any aspects of cell and genomic research. The term HeLa was widely used in the scientific literature over the next several decades but, according to Beskow it was not until 1973 that it was associated publicly with the Lacks name. Over the next 35 years there was extensive discussion in both the lay and scientific press about the massive advances made in medical research because of work with HeLa cells and about the 'ethical' issues around informed consent, privacy, confidentiality, ownership of so-called 'biospecimens', trust in biomedical research and disparities with respect to race, poverty and health. I refer to the Skloot and Beskow papers mentioned above, and also the essay by Schulman[94] for details of these discussions up to the time frame of around 2015-16.

During the period towards the end of the twentieth century, the 'official position' within the US government, and specifically the Office for Human Research Protections, was being formulated, first by the establishment of the National Commission for the Protection of Human Subjects in 1974 through the 'National Research Act'[95] and the publication of the Belmont Report by this Commission in 1979[96]. During the following 10 years the Office reviewed and revised their recommendations, publishing the so-called "Common Rule" in 1991[97].

[94] Schulman AN, What is the body worth? *The New Atlantis*, 2012, 35: 99-115. jstor.org/stable/43152724.
[95] US Government "National Research Act". Public Law 93-348-July 12th 1974.
[96] US Government Department of Health and Human Services, "The Belmont Report" – Ethical Principles and Guidelines for the Protection of Human Subjects of Research, April 18th1979.
[97] US Government, Department of Health and Human Services, "The Common Rule", 1991, 45 CFR part 46.

In part because of the controversies over the treatment of the Lacks family, and also because of several other contentious ethical issues arising at the same time, the Common Rule was revised in 2015 and a Notice of Proposed Rulemaking (NPRM) was issued[98]. Part of the urgency over this debate concerned the publication of the whole genome of the HeLa cell line in a scientific journal[99]; this received widespread criticism in both lay and scientific press, since the Lacks family were not given warning of this, and their genetic information was now freely available on the Internet. The NPRM sought to obtain comments on the protection of human subjects while facilitating valuable research, reducing burden, delay, and ambiguity for investigators. On the basis of the comments received, the government issued a 'Final Rule' in 2017[100], which is apparently still under further consideration. In the language of the document, the Final Rule prescribes 14 '*elements for broad consent to be legally effective'*. With reference to the issues discussed in this book, these elements incorporate the principles that individuals from whom tissues are derived should control the uses of their identifiable biospecimens and identifiable data 'to some extent' but does not substantially change researchers' preexisting ability to make use of de-identified specimens or data.

This doesn't necessarily shed light on the core issue of ownership of parts of the body, and indeed the critical issues have focused on actual or assumed consent for the use of genetic data, and whether payment should be made. Some interesting issues that pertain to the ethics of this matter have arisen, including the fact that Henrietta Lacks was a descendant of slaves and that since she received treatment (albeit unsuccessful) for her cancer free of charge (because of poverty) she was, *de facto*, paid for the donation of her tissues. Reading through masses of literature on this subject, one is left with the view that the patient had 'some degree' of ownership of her tissues but this was not absolute, and the medical profession has a right to seek the use of such tissues for the better good. This is consistent with some of the philosophical and religious that we do not absolutely own our bodies but are guardians of it during life, being prepared, during or after life, for our bodies to be used for the benefit of mankind, giving it due respect.

3.3.1.3.1 Moore and the University of California

John Moore, a resident of Seattle, was referred to the University of California at Los Angeles (UCLA) Medical Center when he was diagnosed with hairy cell leukemia in 1976. This is a rare disease, a form of cancer of the blood and the only treatment at that time was removal of the spleen. This took place successfully, with Moore signing a standard consent form. Over the following seven years, at the request of his treating physician Dr. Golde, he travelled to Los Angeles more than 10 times for follow-up, blood samples being taken each time. On one visit, in 1983, he was asked to sign a consent form that allowed for use of his blood for research purposes. Moore claimed later that he did not give this authorization but that he was pressurized to do so. In March 1984 a patent was issued to Dr. Golde and his assistant, assigned to the University of California according to their rules, the subject of which was the "Mo cell-line". The patent holders then entered into agreements with Genetics Institute and Sandoz Pharmaceuticals, by which time 9 products had been developed on the basis of the Mo cell-line, derived solely from Moore's tissue. The details summarized in this section are taken from various parts of the legal proceedings that were initiated in 1988, widely referred to as 'Moore v The Regents of the

[98] US Government, Department of Health and Human Services, "Notice of Proposed Rulemaking", 2015, Federal Register/Vol. 80, No. 173/Tuesday, September 8, 2015/Proposed Rules

[99] Landry JJM, Pyl PT, Rausch T, *et al.,* The genomic and transcriptomic landscape of HeLa cells, *G3:Genes, Genomes, Genetics* 2013;3(8):1213-24. doi:10.1534/g3.113005777.

[100] US Government, Department of Health and Human Services, "Final Rule", 2017, Federal Register/Vol. 82, No. 12/January 19th, 2017/Rules and Regulations.

University of California'[101]. An extensive discussion in the legal proceedings, through to an opinion by The Supreme Court of California[102], has been provided by Dorney[103].

The original complaint was that, since Dr. Golde would benefit considerably from stock options given to him by Genetics Institute, the defendants proceeded with a lack of informed consent, breach of a quasi-contract, breach of the implied covenant of good faith and fair dealing, intentional infliction of emotional distress, negligent misrepresentation and so on, with the overarching allegation of conversion, a tort that applies when someone intentionally interferes with personal property belonging to another person. A lower appellate court had found in favor of Moore on the conversion issues, citing "*The rights of dominion over one's body, and the interests one has therein, are recognized in many cases. These rights and interests are so akin to property interest that it would be subterfuge to call them anything else"*. However, the Supreme Court disagreed, allowing the complaint of action for breach of fiduciary duty or lack of informed consent, but not for conversion.

This ruling (bearing in mind that it was reached several decades ago when such forms of biotechnology were in their infancy) attempted to protect individual autonomy in the light of new scientific discoveries while encouraging innovation that is of benefit to many people. The real implications, not surprising since they represent an American position, are more relevant to the financial aspects than those of ownership. The emphasis was on the need for more transparent informed consent, which should include the provision that individuals should be told of potential commercial applications of research performed on their tissues. The Court considered, but did not opine on, the issue of whether an individual has the right to sell their own tissue. This lack of a position of ownership but the emphasis on who can make money out of tissues still pervades US law today. Shuster wrote[104], in 2017, '*United States' laws avoid designating human tissue and its by-products as 'property'; however, their economic value is significant in drug and therapy development*'.

3.3.1.3.3 Other Cases

A subsequent interesting case occurred in 2007 when the Eighth Circuit Court of Appeals in the United States had to decide on the ownership of biological materials contributed by individuals for the purpose of genetic cancer research at Washington University[105]. A urologist researcher, Dr. Catalona, collected samples of biological materials from patients for prostate cancer research and sought to transfer those materials when he moved to a different institution. The court determined that Washington University 'owned' the biological material rather than Dr. Catalona or any of the contributing individuals.

In Canada, an action decided by the Superior Court of Justice in Ontario[106], initially concerned with a claim of medical negligence related to the genetic testing of liver tissue taken from a subsequently deceased patient, had to address who owned to liver tissue taken from the patient. The Judge made the following points (abbreviated for 'clarity'):

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[101] Moore v The Regents of the University of California, 215 Cal. App.3d 709,769,249 Cal Rptr 494,531 !988.

[102] The Supreme Court of California, No S006987, July 9, 1990, John Moore, Plaintiff and Appellant, v. The Regents of the University of California *et al.*, Defendants and Respondents.

[103] Dorney MS, Moore v. The Regents of the University of California: Balancing the need for biotechnology innovation against the right of informed consent, *High Technology Law Journal* 1990;5(2):333-69. Hdl.handle.net/10822/542578.

[104] Shuster BK, In the wake of Henrietta Lacks: Current U.S. Law and policy on control ad ownership of one's body tissues used in medical research, *Journal of Health Ethics Administration* 2017;3(2):8-18, doi:10.22461/jhea.1.71614.

[105] Washington University v Catalona, 409 F.3d 667 (8th Cir.2007).

[106] Piljak Estate v. Abraham, 2014 ONSC 2893 (CanLii) Court file no: CV-11-433289.

- *"Rule 32.01 permits only 'the inspection of real or personal property' - is a tissue sample taken from a human being for the purpose of diagnostic testing 'personal property'"*
- *"In my view, this is not a simple question. Neither party has provided me with any jurisprudence determining that issue and neither party has presented a principled approach to determining that question".*
- *"All definitions of property involve ownership or other legal rights with respect to a thing or object. 'Property has been defined as a 'thing belonging to someone'. It is described as 'that which belongs exclusively to a person; in a legal sense, the aggregate of rights that are subject to ownership'".*
- *"Personal property is that class of property dealing with rights in a chattel or any movable or intangible thing that is subject to ownership and not classified as real property",*
- *"The authors state that it 'is unquestionably true that patients own their own tissue before it is excised', and while it has never been squarely dealt with by a Canadian Court, they conclude that diagnostic tissue, once excised, becomes a 'component of the medical record – possession and ownership are transferred to the institution."*

It was therefore concluded that, as with the Catalona case, the excised tissue belongs to the hospital where it was derived. To add some confusion here, a case in the UK[107] determined that when 6 men who were to undergo chemotherapy had donated their sperm for future use should their fertility be compromised, and who sued the storage facility when there was a malfunction that destroyed the sperm, sperm was to be considered as property and that property was legally owned by the individual men. In South Africa, legal and academic positions on tissue ownership have recently been hotly debated[108,109,110], there being no overarching court decision on this. Authors tend to consider common law as the basis for their conclusions, a reasonably common position being that the law has traditionally regarded the human body and its parts as *res extra commercium*, that is outside the commercial sphere, while separated bodily materials are *res nullius*, belonging to no one, until they are brought under the control of the first person who obtains possession of them.

3.3.1.3.4 Overall Conclusions about Ownership

(To be completed, Q1, 2024)

3.4 COMMODIFICATION OF TISSUES AND ORGANS

Commodification, a rather ugly word, generally means the process by which an entity is transformed into an object of trade. The entity can mean anything, such as a service, an idea, or a part of the human body. The concept of trade usually incorporates a payment; with parts of the body this implies that payment is made for the supply of these components, which in theory could include blood, sperm, cells, tissues, or whole organs. Some aspects of this have obviously been alluded to in the above section, but here we focus on the payment rather than the ownership.

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[107] Yearworth v North Bristol NHS Trust [2009] EWCA Civ 37, [2010] QB 1, [2009] 3WLR 118, [2009] 2 All WR 986 CA.

[108] Mahomed S, Nothling-Slabbert M and Pepper MS, The legal position on the classification of human tissue in South Africa: Can tissue be owned? *South African Journal of Bioethics Law* 2013;6(1):16-20. doi:10.7196/SAJBL.258.

[109] Jordaan DW, Social justice and research using human biological material, *South African Medical Journal,* 2016;106(7):678-80. doi:10.7196/SAMJ.2016.v10617.10552.

[110] Mahomed S, Nothling-Slabbert M and Pepper MS, Ownership and human tissue – the legal conundrum: A response to Jordaan's critique, *South African Medical Journal* 2017;107(3):196-8. doi:10.7196/SAMJ.2017.v10713.12062.

Starting with organ transplantation, in the USA, the purchase of organs is strictly prohibited by the National Organ Transplant Act, initially enacted in 1984 and variously modified since then[111]. This does not mean that transplantation of organs does not take place within a fiscal environment but has to exclude actual payment of a donor or the family of a donor, this being intended to avoid people in financial hardship offering their own organs (e.g., a kidney or part of a liver) in order to alleviate that hardship. A similar system applies to the member states of the European Union: "*Member States shall ensure that donations of human organs from deceased and living donors are voluntary and unpaid*"[112].

As discussed and explained by McQuoid-Mason,[113] South African law on these matters has developed over the last 35 years, the 2012 revision being current[114] . This Act also makes it an offence for a donor of tissue, a gamete, blood, or a blood product to receive financial or other reward for such donation except for reimbursing their reasonable costs incurred. It is an offence to sell or trade in such tissues. Notwithstanding such laws, there have been problems with illegal transplantation of kidneys from living donors in countries such as South Africa. It is difficult to write authoritatively about this practice since most information is published by the media rather than serious academic journals. Over a period of many years in the early 2000s it appears that an international kidney trade syndicate operated in South Africa, where recipients of kidneys were generally wealthy Israelis who paid up to $120,000 for a kidney and the donors were usually poor Brazilians who were flown to places such as Durban and paid $20,000 to donate one of their kidneys[115]. Legal action was undertaken[116], with surgeons and doctors being among those indicted but the cases were prolonged and, although some institutions and individuals did confess their guilt, they were eventually ruled out because of procedural irregularities and evidential difficulties. Such practices are still reported, with some hospitals advertising for living donors, or families of recently deceased relatives. For a recipient, price lists vary from Rand 3,545,000 (US$ 200,000) for a kidney to Rand 140 per square centimeter for skin.

There are some strong arguments in favor of an organized market for organs for transplantation. In 2016 the Associated Press ran an article about the situation in Iran, which, as far as I can see, is the only country that officially allows such a market[117]. Iran started a kidney transplant program in 1967, but many wealthy Iranians with kidney failure travelled to the USA or Europe for treatment. The 1979 Islamic Revolution and the costs of the Iran-Iraq war made this very difficult, and the supply of donor organs in the country was insufficient to meet the demand. The current official organ transplantation scheme was started in 1988, where the government pays for the surgery and gives compensation to the donor, around $5,000; non-profit groups handle the arrangements. The result is a very small transplant waiting list and the release of quite a few individuals from poverty. The World Health Organization have consistently

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[111] United States of America, Federal Regulations, Title 42: Public Health, Part 121—Organ Procurement and Transplantation Network, 63 FR 16332, Apr. 2, 1998, as amended at 64 FR 56658, Oct. 20, 1999; 72 FR 10618, Mar. 9, 2007.

[112] Commission of the European Communities Directive of the European parliament and of the Council on Standards of Quality and Safety of Human Organs Intended for Transplantation {COM(2008) 819 final} 2008/0238 (COD).

[113] McQuoid-Mason D, Human tissue and organ transplant provisions: Chapter 8 of the National Health Act and its Regulations, in effect from March 2012 – what doctors must know, *South African Medical Journal* 2012;102(9):733-5. doi:10.7196/SAMJ.6047.

[114] South Africa Government Notice R180 of the Government Gazette No 35099, 2nd March 2012; Regulation 2 Regarding the General Control of Human Bodies, Tissue, Blood, Blood products and Gametes.

[115] Khosa S, The human organ trade – the South African tragedy, South African Journal of Bioethics Law, FORUM Dec 2009;2(2):46-7.

[116] Allain J, Trafficking of persons for the removal of organs and the admission of guilt of a South African hospital, *Medical Law Review* 2011;19(1):117-22, doi: 10.1093/medlaw/fwr001.

[117] Associated Press, In Iran, a unique system allows payments for kidney donors, August 25, 2016.

argued against a commercial market for organs, and indeed tissues of any type[118]. However, serious contrary views have been expressed, for example by the Economist Nobel Laureate Alvin Roth, who has suggested that a controlled market in such organs could be of benefit in the USA[119]. Several eminent philosophers and bioethicists discussed the questions in 2003, largely with reference to living kidneys. Erin and Harris[120] and Savulescu[121]argued strongly for strictly regulated and highly ethical markets for live donor organs, but Richards[122], while recognizing the societal benefits, highlighted the considerable difficulties. In a view from a small country in Africa (Lesotho), Koali[123] presented the positions of both deontology (the position that morality of an action should be based on whether that action itself is right or wrong under a series of rules) and Ubuntu[124] (way of life that finds its roots and meaning in humanity, shaping African cultural, political, and ethical actions). He argued that deontology determined that the payment for human organs is considered immoral because it uses human beings as commodities for others to earn their living, deteriorating human dignity to the level of commodities. Coming from quite a different direction, Ubuntu encourages positive relationships that show respect to humanity as a whole within a community; however, an organ transplant trade is seen to be detrimental to members of the community since it promotes human trafficking and greed.

Of course, there are many individuals and organizations that have given their own positions on commodification of parts of the body; this is a prime example of the importance of ethical discussions where there are many conflicting views and no absolute right answers. Mahoney argued, in 2000[125], that markets in human tissue already exist and cannot be stopped: "*avoiding market and property concepts in transplantation will not eliminate the pursuit of financial rewards for transactions in human tissue but will only obscure them and make critique of the system more difficult*". It is without doubt that existing organ markets can bring considerable profit to many, but donors of the tissues are systematically excluded from the profit; this is the essential argument as to why donors should not be excluded. Some of the more esoteric aspects of the philosophical arguments were explained by Stempsey in 2006[126]. Not surprisingly, a number of books intended for the lay reader have been published on this subject, including those of Goodwin[127] and Andrews and Nelkin[128]; these provide numerous case histories and useful information even if, as titles suggest, they are somewhat sensational.

Moving away from organs to tissues and blood / blood products, similar arguments and controversies pertain, although perhaps not with the same passion as for vital organs. Blood donation is obviously a

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[118] Pirnay J-P, Vanderkelen A, Zizo M *et al*., Human cells and tissues: the need for a global ethical framework, *Bulletin, World Health Organization,* 2010;88:870-2. doi:10.2471/BLT.09.074542.
[119] Roth, AE, Who Gets What and Why: The New Economics of Matchmaking and Market Design, Eamon Dolan/ Mariner Books, 2016, ISBN 0544705289.
[120] Erin CA and Harris J, An ethical market in human organs, *Journal of Medical Ethics* 2003;29:137-8. doi:10.1136/jme.29.3.137.
[121] Savulescu J, Is the sale of body parts wrong? *Journal of Medical Ethics* 2003;29:138-9. doi:10.1136/jme.29.3.138.
[122] Richards JR, An ethical market in human organs, *Journal of Medical Ethics* 2003;29:139-40. doi:1136/jme.29.3.139.
[123] Koali S J, Organ transplant trade: A moral examination, *Open Journal of Philosophy,* 2015;5:261-7. doi:10.4236/ojpp.2015.55033.
[124] Kruse, S, The uBuntu Girl, Face2Face, South Africa,2014
[125] Mahoney JD, The market for human tissue, *Virginia Law Review,* 2000;86:163-223.
[126] Stempsey WE, Religion, philosophy and the commodification of human body parts, *DePaul Law Review* 2006;55:3 art 6, via.library.depaul.edu/law-review/vol55/iss3/6.
[127] Goodwin, Michele, *Black Markets: The Supply and Demand of Body Parts*, Cambridge University Press, New York, 2006. doi:1215/03616878-2007-049.
[128] Andrews L and Nelkin D, *Body Bazaar: The Market for Human Tissue in the Biotechnology Age*, Crown Publishers, New York 2001. ISBN 0609605-402.

world-wide phenomenon but with different levels of central control and the financial implications. As discussed by Petrini in an essay on the conflict between altruism and commercialization with blood[129] , while the vast majority of regulations and guidance indicate that the donation of blood should be voluntary and unremunerated, this does not preclude the possibility that donors receive some form of reimbursement, that subsequent procedures may involve considerable financial activity, that legislation in some nations may allow trade in certain types of human biological material and that voluntarily donated human blood may be used to derive products that are subsequently marketed. Once some sort of market is legally permissible, all types of challenge, including improper handling of finances and lack of adherence to quality standards, will be faced. Some of these were discussed by Pirnay *et al* with respect to the handling of human cells, tissues, and cellular and tissue-based products with the European Union[130]. One of the major points here was the potential disadvantage of having pharmaceutical industry-type quality regulation imposed on this emerging biotechnology industry. There is ample evidence, however, that without the strictest of controls and adherence to the highest moral standards, contaminated material can readily be transmitted from donor to recipient, leading to serious infection and death. A very serious issue arose in France for example, over several years, with the infection of children with Creutzfeldt-Jakob disease through the use of contaminated human growth hormone, with extensive subsequent litigation and charges of involuntary homicide[131]. A good discussion of the American perspective here was published by Greenwald *et al* in 2012[132].

The profit motive plays a very significant part in the potential for short-cuts in this industry. This aspect has been addressed, but only marginally, in the USA within the Uniform Anatomical Gift Act and its various modifications over the years[133]. With respect to the tissue engineering component of regenerative medicine and the quest to reconstruct the body, one of the more relevant aspects here has been the source of cells used in tissue regeneration, although this is rarely controversial except for the situation with embryonic stem cells, which I shall deal with elsewhere. As described by Naughton[134], who initially concentrated on tissue-engineered skin within the US company Advanced Tissue Sciences, Inc., the development of human fibroblast-based tissue engineering, with cost-effective large-scale production "off-the -shelf" constructs requires an adequate source of health cells.; differentiated allogeneic cells are the most popular for this purpose and at the time of the greatest interest in the early 2000s, neonatal foreskin was the preferred source. Foreskin is usually regarded as medical waste and, provided regimes for safe disposal are followed, there are no constraints over the commercial transactions that subsequently take place. The internet, and especially parts of social media, contributes significantly to this trade and the controversies that surround it, which are not discussed here. It is obvious that foreskin tissue is not only used for tissue engineering but also for many cosmetic products[135], where profit margins are enormous.

One final comment on the ethical issues around commodification of allogeneic tissue in tissue engineering. We have seen that in most cultures, the donation of tissues, especially those that are no

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[129] Petrini C, Between altruism and commercialization: some ethical aspects of blood donation, *Ann 1st Super Sanita* 2013;49(4):412-6. doi 10.4415/ANN_13_04_16.

[130] Pirway J-P, Vanderkelen A, Ectors N, *et al.*, Beware of the commercialization of human cells and tissues: situation in the European Union, *Cell and Tissue Banking* 2012;13:487-98. doi 10.1007/s10561-012-9323-3.

[131] Spurgeon B, French doctors are tried for treating children with infected growth hormone, *British Medical Journal* 2008;336(7640):348-9. doi: 10.1136/bmj.39489.717292.C2.

[132] Greenwald MA, Kuehnert MJ and Fishman JA, Infectious disease transmission during organ and tissue transplantation, *Emerging Infectious Diseases* 2012;18(8):e1. doi:10.3201/eid1808.120277.

[133] Martinez, B, Uniform Anatomical Gift Act (1968), Embryo Project Encyclopedia (2013-08-05), ISSN 1940-5030, http://embryo.asu.edu/handle/10776/6048.

[134] Naughton GK, From lab bench to market; critical issues in tissue engineering, *Annals of the New York Academy of Sciences* 2002;961:372-85. doi:10.1111/j.1749-6632.2002.tb03127.x.

[135] Oliveira T, Costa I, Marinho V, *et al.*, Human foreskin fibroblasts: from waste bag to important biomedical applications, *Journal of Clinical Urology* 2018;Feb 26. doi:10.1177/2051415818761526.

longer of value to the donor, is considered to be essential for the good of the community at large, and there should be no expectation of financial benefit to the donor. This was the prevailing view in the regenerative medicine community at the time. However, as Boyce and Lalley have recently pointed out[136], although some uses of acellular dermal substitutes and autologous cell products have had some successes, overall performances, especially with allogeneic products, is far from satisfactory because of deficiencies of hypopigmentation, the absence of stable vascular and lymphatic networks, absence of hair follicles, sebaceous and sweat glands and incomplete innervation. In other words, the "altruistic" donation of foreskin for the "common good" has so far been a failed equation.

And for completeness in these murky areas of immorality, no rules can prevent abhorrent acts from medical professionals, and few rules can absolutely defend against very bad taste, especially when it pretends to be in the name of art. A prime example of the former situation was uncovered in my own university in Liverpool, UK. There is no conflict of interest to report here, but for full disclosure, I was Pro-Vice Chancellor (Vice Provost) of the university during some of the time when the events unfolded, but without any involvement in or knowledge of the events. To cut a long story short, a pathologist in the Alder Hey Children's Hospital in Liverpool, Professor van Velzen, collected and stored vast numbers of organs from deceased children without any informed consent. A massive amount of evidence was obtained dealing with some 20 areas of malpractice by the professor, the final "Redfern Report" concluding that many personnel in the hospital and university, and indeed in the coroner's office, shared in culpability[137]. Part of the 'rationale' for organ collection concerned future research into the pathology of the diseases, and into methods for cure (ostensibly including reconstructive surgery), although none of this actually took place. Pathological practices, and medical research in general, in the UK were affected by these outcomes.

With respect to art, I have to mention in passing some exhibitions that include body parts. As described by Burns back in 2007, the BODY WORLDS exhibition toured the USA in which preserved human cadavers were 'posed and exposed' to educate the public[138]. The BBC in Australia[139] reported on a major controversy in Sydney when a 'Real Bodies' exhibition was shown, which included cadavers provided by a medical university in China, with claims by the organizers that these were simply 'unclaimed corpses' while demonstrators claimed them to be executed political prisoners. This is not what I had in mind in relation to the artistic dimensions of reconstructing the body, and no images are provided here.

3.5 HEALTH ECONOMICS, HEALTH DISPARITIES

(To be completed, Q2, 2024)

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[136] Boyce ST and Lalley AL, Tissue engineering of skin and regenerative medicine for wound care, *Burns Trauma* 2018;6:4. doi:10.116/s41038-017-0101-y.
[137] Hunter M, Alder Hey report condemns doctors, management and coroner, *British Medical Journal,* 2001;322(7281):255. doi:10.1136/bmj.322.7281.255.
[138] Burns L, Gunther von Hagen's BODY WORLDS: Selling beautiful education, *American Journal of Bioethics* 2007;7(4). doi:10.1080/15265160701220659.
[139] BBC New Sydney Australia, "Real Bodies; exhibition causes controversy in Australia, 26th April 2018.

3.6 THE REGULATION OF MEDICAL TECHNOLOGY

(To be completed, Q2, 2024)