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The legal and ethical considerations relating to the supply and use of human tissue for biomedical research: A UK perspective

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Abstract Alder Hey Children's Hospital supplied parts of the thymus gland removed from young children during heart surgery to a pharmaceutical company. The circumstances raised a number of very serious issues to the medical research community and have led to a consideration of the legal and ethical framework in which human tissue is used for medical research. The use of human tissue has become an increasingly common feature of the drug discovery and preclinical research process in the last decade. This is because, as the understanding of human biochemistry increases, it is important to study the biochemistry of drugs in the tissue in which they are intended to act. The use of animals is currently the subject of much debate, but if the need for animal experiments is to be reduced more reliance will have to be placed on experiments based on the use of human tissue. Several problems have been encountered in this area over the last few years. These include the retention of organs by Bristol Royal Infirmary and the Alder Hey Hospital but also the more bizarre case of Anthony-Noel Kelly, an artist who had acquired body parts for use in his sculptures. This has been an area of some debate for several years and the historical precept that the body of a deceased person could not be owned has been considered in relation to the use of the human tissue in research. The debate about the ownership of human remains as such is not reviewed, but the current case law is applied to the use of human tissue both in the context of treatment and in research.

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Use of tissue

The direct use of donated human tissues for transplant, for fertility treatment and, in certain cases, to aid in disease diagnosis are well-established practices, and are all

subject to regulation through legislation. However, such routine uses only evolved following considerable human tissue-based research. It is interesting therefore that the legislation covering the use of human material for research is sparse, and until

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relatively recently, there were no generally accepted guidelines or codes of practice. Historically, most research on human tissue, whether removed surgically or *post mortem*, was related to developing the above clinical uses, or in uncovering the aetiology of human diseases. As such, it was undertaken primarily within the hospitals within which those tissues originated, or within associated medical schools, and ethical control was regarded as very much a local issue, and was often characterised by *ad hoc* arrangements between researchers and particular surgeons and pathologists. However, there has been a growing awareness of the value of human tissue for research both within the academic medical community and within the commercial sector, and the increased requirement for donated human tissue has resulted in a clear need for generally accepted ethical guidelines covering acquisition and use. Such guidelines were first provided in 1995 by the Nuffield Council on Bioethics in their publication 'Human Tissue: Ethical and Legal Issues',¹ and subsequently by the Royal College of Pathologists (2001)² and the Medical Research Council (2001).³

Probably the highest profile area of growth in human tissue research is in pharmacogenomics, where companies such as DeCODE in Iceland and Oxagen in the UK are genotyping large numbers of individuals, in some cases whole populations. The value of this information is in identifying associations between genetic make-up and disease susceptibility, disease diagnosis and drug responsiveness. In concept, this approach is very simple, in that it requires only a single sample, usually blood, from each individual, and from that the researcher has access to the individual's DNA, from which specific genotypic mutations or polymorphisms can be identified. Such genotypic features may then be associated with known features of the donor's medical history, and links between genotype and pathology identified.

Another major area of growth is in the use of human tissues for drug discovery and development research. A major reason for this has been the poor performance of the

pharmaceutical industry in bringing new medicines to market. This is due at least in part to a historical over-reliance on data derived from animal experimentation, and it is becoming ever more obvious that experimental animals can provide highly misleading results when used as surrogates for humans. Such a situation led to the founding of Pharmagene, a drug discovery company that uses only donated human tissues for its drug discovery and development activities. Pharmagene is by no means unique in using human tissue for drug discovery research. As such it provides a useful model for study of the range of issues facing would-be researchers, and of the range of potential uses to which human tissues can be put.

Pharmagene has established a network of suppliers of human tissues, hospitals and associated tissue banks, through which it acquires tissues from all the main organs of the body, and to which it applies a number of relevant technologies, from gene expression to pharmacology and toxicology. The human tissues used can serve a number of purposes, for example, they provide information on the distribution, the abundance and the functional role of drug targets (receptors, enzymes, ion channels, etc.) around the body in health and disease. The technologies employed include specific mRNA detection, specific protein detection and functional (biochemical and pharmacological) profiling. This allows researchers to identify which human tissues are likely to respond to which drugs, whether in a beneficial or detrimental manner. Although the use of isolated human tissues allows the generation of information relating to the potential utility of new drugs in combating human diseases, it can also provide other valuable information including side-effect liability, drug absorption from specific areas of the gastro-intestinal tract, potential drug-drug interactions and cellular toxicity.

Of the various research uses of human tissue, arguably the most important is 'functional profiling', that is identifying which human tissues actually respond to a drug of interest, and in what way. Although

most donation for research follows surgical removal of tissues for medical reasons, much is from cadavers, and despite the fact that a donor may have been dead for a number of hours, this does not necessarily mean that all the tissues from that donor are themselves dead. Indeed, under appropriate conditions, many tissues can live for hours or even days *post mortem*. This means that not only tissues removed during surgical procedures, but also those removed *post mortem* can be used in testing the body's responsiveness to novel drugs before embarking on the hugely expensive full development programme that is necessary to permit the testing of that new drug in humans.

Ownership of tissue

The problem of the ownership of tissue is one that has exercised the courts for many years. In one leading case *Dodewood v Spence*,⁴ the subject matter was a preserved two-headed foetus which had been acquired by the appellant for display. It had been seized by the police and he was suing for its return. In that case in the High Court of Australia, Griffiths CJ expressed the opinion that;

when a person has by the lawful exercise of work or skill so dealt with a human body in his lawful possession that it has acquired some attributes differentiating it from a mere corpse awaiting burial, he acquires a right to retain possession of it, at least against any person not entitled to have it delivered to him for the purpose of burial

It is arguable that, as a person only attains legal status at birth, the foetus, being still-born was not the body of a person but this is not the approach taken by the Griffiths CJ. Also, in the case of *Dobson v North Tyneside Health Authority*⁵ it was held that the family of a woman who had died of a brain tumour was not entitled to the property in or possession of the preserved brain. The brain had been removed and preserved on the orders of the coroner but subsequently lost or destroyed. It may be that this case was dependent on its facts as the action was

brought by a relative of the woman who wanted the brain for evidence in a medical negligence action. Peter Gibson LJ was careful in his judgment. He did not say specifically that the brain could not be the subject matter of property itself but he did hold that he could not see how the fact that the brain was fixed in paraffin could render it an item over which the relatives ever became entitled to claim possession for the purpose of interment or any other purpose, still less that the relatives ever acquired property in it. This finding covers two elements – could the tissue ever be the subject matter of property and, if so, who was the owner of the tissue? The carefully worded judgment neatly avoids the first question on the basis that the relatives were not entitled to property in or possession of the brain.

The case of *R v Kelly*⁶ gives a far greater insight. Kelly was an artist who had access to the Royal College of Surgeons where he was permitted to draw anatomical specimens, which were used by doctors training to be surgeons. He asked a technician to remove some specimens, which he then used for making casts. Kelly was found guilty of theft (which requires the dishonest appropriation of property belonging to another) and appealed on a number of grounds, one of which was that the finding by the Judge that the body parts were capable of being property was wrong. The Court of Appeal held that the Judge was correct in holding that:

as a matter of law there is an exception to the traditional common law rule that 'there is no property in a corpse', namely that once a human body has undergone a process of skill by a person authorised to perform it, with the object of preserving for the purpose of scientific or medical examination or for the benefit of medical science, it becomes something quite different from an interred corpse. It thereby acquires a usefulness or value. It is capable of becoming property in the usual way and can be stolen.

The Human Tissue Act 1961 provides a statutory framework for

the use of parts of bodies of deceased persons

for therapeutic purposes and purposes of medical education and research and with respect to the circumstances in which post-mortem examinations may be carried out and to permit the cremation of bodies removed for anatomical examination.

The key provision of the act is that where a person expressed a request in writing or orally before two witnesses that his body or specified part of it be used for therapeutic purposes or medical education or research the person lawfully having possession of it after his death may authorise the removal of any part or the part specified by the person for such uses. In fact the person lawfully in possession of the body can authorise the removal where he had no reason to believe that the deceased person or his relatives had or have any objection to the relevant use being made. The act does not refer to the ownership of the body or the tissue removed. The removal has to be undertaken by a qualified medical practitioner.

The cases cited above all deal with the question of dead bodies, and not tissue donated by or acquired from living people. It seems to us that it would be difficult, given the possession and control exercised by people over their own bodies to argue that the living person did not, for all practical purposes, own their own bodies. However, this raises some serious human rights issues, which we do not have space to deal with here. Society does place constraints on what people can do to their own bodies when legislating against practices it considers deviant or immoral (such as slavery) or in respect of those who are incapable of making properly informed decisions for themselves. The Human Organ Transplant Act 1989 which among other things prohibits the commercial dealing with human organs (but not regenerative tissue) is one example. As the scope of this paper is limited to research this legislation is not reviewed in detail.

There is some debate about the proprietary interests in human tissue obtained from living people. One view is that when tissue is excised, the patient has abandoned the tissue and it immediately becomes the property of the hospital or

surgeon removing the tissue. It appears to us that a key element of abandonment is that the person abandoning the tissue must have given up all interest in it. As can be seen to the reactions from the parents in relation to the retention of tissue at Bristol Royal Infirmary and the Alder Hey Hospital, people care very much about what happens to tissue that is taken, albeit that in these cases the reaction came from the parents of the children. Moreover, it seems to us that the seeking of consent to future use of tissue must recognise at least some continuing interest in the tissue on the part of the patient. While strictly this may not relate to the property rights in the tissue, the proprietary issue are inextricably linked to the ethical ones. An analysis of the law is given in the Nuffield Council on Bioethics report.¹ However, the Nuffield Council's conclusions contain the following recommendation:

we recommend that the law should proceed on any claim over removed tissue by examining the basis of the consent given to the procedure that resulted in the removal of the tissue. In particular, it should be regarded as entailed in consent to medical treatment that tissue removed in the course of medical treatment will be regarded as abandoned by the person from whom it was removed.

We feel that, in view of recent events in Bristol and Alder Hey it is now time to reconsider the basis on which tissue is obtained. In fact the recent MRC guidance³ takes the view that it is preferable that tissue given by live donors should be considered as a gift rather than abandoned and this position reflects a more generally held view that has developed over the last few years. This vests clear title to the tissue in the recipient and can place conditions on the gift. Hence, if consent has to be sought, ideally the form of consent should provide that the tissue is given to the hospital or researcher for the relevant uses. The consent should also be clear as to whether the use will be commercial or solely non-commercial.

The issue of ownership of tissue taken from a living person has been considered by

the Supreme Court of California in the *John Moore* case.⁷ John Moore had hairy cell leukaemia and had his spleen removed. The physician retained the spleen and used it to create a cell line that was of significant value. John Moore sued for conversion and lack of informed consent. Ultimately the Californian Supreme Court held that John Moore did not have a property right in the cells taken from his body.

Consent

As can be seen, a discussion of the legal issues relating to the ownership of tissue has led to a discussion of consent. In our view the issues of consent and ownership are inextricably linked. Even when advocating that tissue be treated as abandoned, the Nuffield Council recommends that the law proceeds on the basis of consent. Article 5 of the Council of Europe Convention on Human Rights and Biomedicine provides that an intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. The person must, before giving the consent, be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The consent can be withdrawn at any time.

In order to be effectively given consent must be given freely. This will require the procedure to be explained to the patient and sufficient steps to be taken to ensure that the patient understands the nature of what is to be done. It would not make sense for this to extend to a detailed explanation of the procedural steps and science behind a biopsy, for example, unless that information is of particular relevance to the patient. In the Nuffield Council report,¹ the section on consent considers the expressions 'informed consent' and 'fully informed consent'. In the section titled 'Caveat on consent' it states that the requirement is not that the consent be complete but that it be genuine. There is detailed analysis in the Nuffield Council report, summarised in the following recommendation:

We recommend that those involved in the removal of human tissue from donors should ensure that the explanation given to the donor is explicit about the range of intended uses of the tissue and about any risks the donor may incur either in having the tissue removed or as a consequence of its removal. Only on these conditions can the consent of the donor, and hence the procedure itself, be valid.

If the consent is being given as part of a clinical procedure it must be made clear to the patient that the consent to the clinical procedure is separate from the consent to the use of the tissue and that, even if the patient does not give consent, his treatment will be identical.

From the legal perspective there have been a number of cases dealing with the obligation to inform the patient when obtaining consent, usually in relation to clinical procedures. Most recently the case of *Pearce v United Bristol Healthcare NHS Trust*⁸ Lord Woolf MR held that if there is a significant risk that would affect the judgment of a reasonable patient, then in the normal course it is the responsibility of the doctor to inform the patient of that significant risk, if the information is needed so that the patient can determine for him- or herself as to what course he or she should adopt.

Ethical considerations

There are a number of ethical and other issues that need to be considered in the use of human tissue for medical research. The patient from whom the tissue is taken does have certain rights including in relation to the protection of their personal data and assessment of their physiology. A clear distinction is drawn between taking tissue from an individual as part of a therapeutic or diagnostic procedure where the ultimate purpose is to benefit the patient and taking tissue from healthy individuals where there is not necessarily any benefit to that person. In the latter case, the practice has long been accepted in the donation of blood but clear issues have arisen, particularly since the advent of AIDS, as to what testing can be

undertaken on tissue and the access that the individual should have to the results.

In both the use of tissue removed as part of a therapeutic or diagnostic procedure and the removal of tissue from a healthy volunteer, properly informed and freely given consent should be obtained. This should extend to the range of uses to which the tissue is put. The MRC guidance states that

wherever practicable individual consent should be obtained for the use for research of human material surplus to clinical requirements. At the very least, for example, patients should be made aware in any surgical consent form that they sign that surplus material may be used for research, and given the opportunity to refuse.

Article 21 of the Council of Europe Convention on Human Rights and Biomedicine provides that 'The human body and its parts shall not, as such, give rise to financial gain'. This constitutes a clear prohibition on the commercial sale of human tissue, a view that is reflected in the MRC Guidelines. The use of tissue for commercial research is not prohibited by this provision provided the tissue as such is not the basis of the commercial transaction. It is our view that the licensing or sale of intellectual property, including data, does not fall within the prohibition. However, it is important to take care in the collecting of tissue because any payments to the researchers collecting the tissue could be misconstrued. It is vital that only reasonably incurred expenses are reimbursed.

The question of the anonymity of a tissue sample must be addressed in any decision to use tissue for research. If a sample is not anonymised then data generated in relation to that tissue would fall within the ambit of the Data Protection legislation in the UK. If it is anonymised then it will be impossible to seek renewed consent to a use of the tissue that was not previously consented to.

It is our view that where tissue is taken in a clinical context the use of the tissue must be approved by an ethics committee. In many cases where tissue is taken in a non-clinical context it may be appropriate to seek

ethics committee approval, depending on the type of tissue involved, the individuals from whom it is to be taken and the use to which it will be put.

There has been much debate about the ownership of intellectual property generated using human tissue. It is important to draw a distinction between the ownership of tissue and the rights generated using the tissue. Tissue and intellectual property are entirely separate types of property. At its creation the first owner of intellectual property is generally that of the creator, so an inventor has the right to apply for a patent and an author is the first owner of copyright. It is only if the creator has an agreement with someone else or has a special relationship with them (ie as an employee) that the owner becomes someone other than the creator. We do not believe that issues relating to the acquisition of human tissue should undermine the ability of those undertaking research to own the intellectual property or to obtain patent protection. The criteria for patentability are set out in the Patents Act 1977. The patentability of biotechnological inventions have been considered in the Biotechnology Directive which has been implemented in the UK, although it is facing difficulties in other member states of the EU. Recital 26 of the Directive provides

Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material has been taken must have had the opportunity of expressing free and informed consent thereto, in accordance with national law.

However, this recital is not reflected in the operative text of the Directive and has not been implemented in the UK.

Conclusion

We have tried to summarise the issues relating to the use of human tissue for research. In the space permitted we have not been able to deal in detail with all of the issues.⁹ For example there are real data protection issues concerning the use of

human tissue if it would be possible to identify the individual from the tissue or data provided with it. This is a complicating factor in the case of rare diseases.

In any arrangement for the collection of human tissue it is important to consider the legal and ethical issues together and to ensure that the relevant issues are understood. It is easy in research to forget the emotive nature of the issues and how people outside the scientific community may take a differing view from those within the community. The key to avoiding problems is to ensure that the donors have freely given consent after having been made properly aware of the issues surrounding the donation of tissue. We believe that when properly informed patients will be willing to allow tissue to be used for research that will benefit society generally.

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5. *Dobson v North Tyneside Health Authority and Newcastle Health Authority* [1996] 4 All ER 474.
6. *R v Kelly* [1999] QB 521.
7. *Moore v Regents of the University of California* (1990) 793 P 2d 479.
8. *Pearce v United Bristol Healthcare Trust* [1999] PIQR p. 53.
9. A very detailed review of the law is given in Annex B of the Interim Report of The Bristol Royal Infirmary Inquiry which can be found at URL: <http://www.Bristol-inquiry.org.uk>

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