

**NUFFIELD
COUNCIL^{ON}
BIOETHICS**

**Emerging techniques to prevent inherited
mitochondrial disorders:
ethical issues**

CALL FOR EVIDENCE

January 2012

Call for evidence

The Nuffield Council on Bioethics is inviting written submissions of evidence to inform its consideration of ethical issues arising from emerging techniques to prevent the transmission of inherited mitochondrial disorders.

How to respond

This is an open Call for Evidence, seeking ethical views on any aspect of these emerging techniques and the issues associated with them. Accordingly, we have not provided structured questions for response.

We would prefer it if you could send your response to us electronically. Responses can be sent via email to Johanna White: jwhite@nuffieldbioethics.org, with '*Techniques to prevent inherited mitochondrial disorders: ethical issues*' in the subject line. Please ensure that you also include a completed response form with your submission, which can be downloaded from: www.nuffieldbioethics.org/mitochondrial-donation.

If you would prefer to respond by post, please send your submission to:

Laura Riley
Nuffield Council on Bioethics
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For information about obtaining a large print version of this call for evidence, please contact us using the below details.

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Fax: +44 (0)20 7323 6203

Website: <http://www.nuffieldbioethics.org/mitochondrial-donation>

Closing date for written evidence: 5pm Friday 24 February 2012.

Web references throughout this document were accessed in January 2012.

Guidance on submitting written evidence

It will assist the Working Group if you could:

- limit your response to one single Word-formatted document, of no more than 2,000 words in length, preferably submitted by email;
- include a short summary in bullet point form at the beginning of the document;
- have numbered paragraphs throughout; and
- ensure that your submission is accompanied by a completed response form, which can be downloaded from www.nuffieldbioethics.org/mitochondrial-donation.

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In addition:

- The Working Group's final report may make public the evidence received during the project in full, or in selected quotation. Please state in the response form whether you wish your submission to be made public.
- If you wish to include private or confidential information in your submission, please discuss this, with the project leader, Laura Riley (lriley@nuffieldcouncil.org) before submitting it.
- Material that has previously been published should not form the basis of your submission.
- If you reference your own previously published work in your submission and feel that the Working Group would benefit from reading it in the published form, please send us electronic or hard copies of the referenced items together with your submission.
- Although your submission remains your own property, the Nuffield Council on Bioethics consider it a courtesy that you do *not* publish your submitted response until after the publication of the final report. This is scheduled for spring/summer 2012. If this expectation raises any concerns, please contact the project leader, Laura Riley (lriley@nuffieldcouncil.org) in advance of your submission.

Nuffield Council on Bioethics

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The Terms of Reference of the Council

- 1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
- 2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
- 3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

Working Group members for this project

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Professor Peter Braude FRCOG FMedSci

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Working Group terms of reference

- (a) to identify and examine ethical issues relevant to the clinical use of techniques of in vitro mitochondrial transfer
- (b) to elaborate these issues with a view to stimulating and informing further discussion, deliberation and debate
- (c) to prepare a report on the above, to be delivered in Spring 2012

About this project

This project will identify and examine ethical issues relevant to the clinical use of experimental techniques to prevent the transmission of inherited mitochondrial disorders, in particular pronuclear transfer (PNT) and maternal spindle transfer (MST). These are not currently permitted for use in treatment in the UK.

The Council aims to contribute information and insight on ethical issues arising from the use of these techniques via a short report which will be published in spring/summer 2012. The findings of the project are intended to stimulate and inform deliberation and debate among the public, professional groups, regulators, policymakers and Parliamentarians.

The emerging techniques¹ which the project primarily examines could be used in combination with in vitro fertilisation (IVF) and gamete donation to prevent children from being born with inherited mitochondrial disorders. At present, there are no known cures for these disorders, which can have mentally and physically disabling symptoms and may cause death in babies, children and young people. Approximately one in 250 live births² and at least one in 10,000 adults in the UK are affected.³ For further information on the effects of these disorders, please see <http://www.nuffieldbioethics.org/mitochondrial-donation/mitochondrial-donation-what-are-mitochondrial-disorders>.

¹ These techniques have been collectively referred to as 'mitochondrial donation' or 'mitochondrial transfer'. There does not yet appear to be a consistently or commonly-used term by which to refer to them.

² Elliott HR, Samuels DC, Eden JA *et al.* (2008) Pathogenic mitochondrial DNA mutations are common in the general population *The American Journal of Human Genetics* **83**: 254-60; Vandebona H, Mitchell P, Manwaring N *et al.* (2009) Prevalence of mitochondrial 1555A-->G mutation in adults of European descent *New England Journal of Medicine* **360**: 642-4; Bitner-Glindzicz M, Pembrey M, Duncan A *et al.* (2009) Prevalence of mitochondrial 1555A-->G mutation in European children *New England Journal of Medicine* **360**: 640-2.

³ Schaefer AM, McFarland R, Blakely EL *et al.* (2008) Prevalence of mitochondrial DNA disease in adults *Annals of Neurology* **63**: 35-9.

Background information

1. What are mitochondria and why are they essential to our health?

Mitochondria are small structures that are present in all the cells of the human body in multiple copies. Mitochondria are found in the cytoplasm, a gel-like substance inside the cell that surrounds the nucleus. Mitochondria produce the energy that each cell in the human body needs in order to function. Serious health problems can arise if we have mutations in the genes contained in the mitochondria, as this affects the energy available to the cell.

According to our current understanding, the 13 mitochondrial genes are only thought to govern the function of mitochondria. The 25,000 genes typically contained in the nucleus of a cell provide the basis for how human bodies are built and for many of our unique personal characteristics.

Many of us have low levels of mutated mitochondrial DNA (mtDNA) in our cells and experience no adverse symptoms. However, when the mutated mtDNA copies make up around 60 per cent or more of the total of mtDNA copies in a cell,⁴ this causes serious health problems. Patients who are affected by mtDNA disorders may have mutations in either some, or all, of the mitochondria in their cells. This often impacts hardest on the organs of the body which require relatively large amounts of cellular energy to function properly, such as the brain, heart, kidneys and major muscle groups.

In the absence of an effective cure, and given the very poor outcomes for some children and young people affected, laboratory research is currently being carried out on techniques to prevent the transmission of inherited mitochondrial disorders. Researchers are investigating options that could be offered to prospective parents seeking to prevent a disease-causing level of mutated mitochondria from being passed on to their children, and who are also wishing to use their own sperm and eggs to have a baby. No licensed technique is currently available which could fulfil both of these criteria.

⁴ Taylor RW and Turnbull DM (2005) Mitochondrial DNA mutations in human disease *Nature Reviews Genetics* **6(5)**: 389-402.

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Experimental techniques such as pronuclear transfer (PNT)⁵ and maternal spindle transfer (MST)⁶ have been developed in response. It is currently unlawful under UK laws governing IVF and embryo research to offer such techniques for treatment, however, the legislation does allow for them to be introduced, subject to Regulations that can be made by the Secretary of State, if approved by Parliament. If they were permitted to be used in treatment, the expectation is that the resulting children would be born free from inherited mitochondrial disorders.

⁵ Craven L, Tuppen HA, Greggains GD *et al.* (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease *Nature* **465**: 82-5.

⁶ Tachibana M, Sparman M, Sritanaudomchai H *et al.* (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells *Nature* **461**: 367-72.

2. Ethical questions arising from techniques to prevent mitochondrial disorders

Some ethical questions which may be considered as part of the project are listed in Box 1.

Box 1: Ethical questions arising

1. Emerging techniques such as PNT and MST involve replacing the mitochondrial genes that a child would have received through natural conception, with mitochondrial genes taken from a healthy donor. Is it acceptable, in this instance, to select genes that will then be inherited by future generations?
2. PNT involves removing the two pronuclei from a very early embryo containing a significant level of mutated mitochondria, at the one-cell stage before the genetic material in the pronuclei of the sperm and egg cells merges to form the mature nucleus of the embryo. The pronuclei are transferred into another embryo at the same stage of development, which contains healthy mitochondria and which has had its pronuclei removed. From the two-cell stage of embryonic development onwards, the embryo's cells contain one nucleus combining both parents' DNA. What ethical distinctions can we make between prospective treatments which would:
 - a. transfer pronuclei between embryos?
 - b. transfer the nucleus of a cell between embryos⁷?
 - c. seek to modify the nuclear DNA of an embryo?
3. All new techniques pass through research stages before being offered for treatment, but in the early stages of treatment might still be considered experimental. Is it reasonable to use experimental techniques such as these in treatment?
4. After the use of these techniques, children would inherit nuclear DNA (around 25,000 genes) from their parents, and mtDNA (13 genes) from the donor of the egg. What might the use of these techniques signify for the relationships of the resulting child to the three adults with whom it shares a genetic connection?
5. How might mitochondrial DNA be associated with a person's identity?

⁷ It does not currently appear that nuclear transfer techniques (similar to those used to produce cloned embryos for research) would be technically the most straightforward to use in the reconstruction of eggs or embryos to render them unlikely to transmit inherited mitochondrial disorders: see Brown DT, Herbert M, Lamb VK *et al.* (2006) Transmission of mitochondrial DNA disorders: possibilities for the future *The Lancet* **368**: 87-9.

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6. Could the relationships created between the people involved in these new techniques- particularly between the mitochondrial donor and a person born with their donated mitochondria- be seen as similar to those involved in:
 - a. organ or tissue transplantation?
 - b. gamete donation?
 - c. a donation of other bodily material?Or, should these relationships been seen as unique?
7. Only daughters born as a result of these techniques would be able to pass their mtDNA on to subsequent generations. Would it be reasonable to permit prospective parents using these technologies to also use pre-implantation sex selection (preferring male embryos), if they requested it in order to limit the risks of transmitting any adverse side effects of the techniques to future generations?
8. If mitochondrial donation were to be approved for medical treatment in the UK, what government or regulatory policies, and/or professional guidelines would be needed to promote ethically sound practices?
9. If mitochondrial donation were *not* to be approved for translation from research into medical treatment in the UK, what ethical concerns, if any, would follow?
10. Is it desirable for a record of the donation to be kept and managed by the relevant authorities, and if so, what should be recorded and to whom should this information be made available?

Why might these ethical issues arise from these techniques?

The nature of the pronuclear and maternal spindle transfer techniques means that any resulting children would be born with nuclear DNA (nDNA) from their parents' sperm and egg, plus healthy mitochondrial DNA (mtDNA) taken from an egg donor who is not related to the mother. The effect of this is that the child would not inherit mtDNA from its mother, as would have happened naturally. This gives the resulting child a genetic connection to three people, albeit with a much smaller genetic contribution coming from the donor.

The law is very clear that an egg donor is not the legal mother of the resulting child⁸ because the legal mother is the woman who carries the child. However, egg donors may take on different social roles in relation to the children born and the recipient families, reflecting the diverse attitudes towards donation found in individuals and families.

⁸ s.47 of the Human Fertilisation and Embryology Act 2008, is headed: 'Woman not to be other parent merely because of egg donation' and follows: '*A woman is not to be treated as the parent of a child whom she is not carrying and has not carried*', before listing some exceptions which would not usually be engaged in this context.

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The genetic link between a mitochondrial donor and the individual created using this donation has a relatively ambiguous social framework by which to contextualise it. There is no direct evidence on which to base assumptions about the perspectives of people born after the use of these techniques regarding any social role of the mitochondrial donor. Similarly it is an open question as to whether the donor giving an egg intending for her mitochondria (rather than her nuclear DNA) to be used might be approaching the donation with different expectations of its social meaning than a donor donating an egg in its entirety may do.

It may be relevant to note when considering the potential social meaning of mitochondrial connectedness, that the genetic link to the mitochondrial donor would be inherited by children descended from girls born via these techniques. This would give rise to a genetic link traceable back up the maternal line to the donor, whether or not she was identifiable. There is an online market for information about mitochondrial heritage but not a great deal is known about perceptions of any social meaning within this genetic relationship.⁹

Society is used to ascribing social meanings to the donation of human tissue according to its context, for example as seen in the different expectations around the subsequent social roles of blood, egg, sperm, or live kidney donors in relation to recipients and their families.¹⁰ The possible ambiguity in the perception of the social relationship between the resulting child and the donating woman that would be brought about after the use of maternal spindle and pronuclear transfer is also seen in the range of language used to describe the parentage of people born after the use of these procedures.

⁹ See, for example, commercial websites: Genetree.com (2012) *Mitochondrial DNA (mtDNA)*, available at: <http://www.genetree.com/mtdna>; Ancestry.com (2012) *Maternal lineage test*, available at: <http://dna.ancestry.com/learnMoreMaternal.aspx>.

¹⁰ See, for example, the Nuffield Council's recent report on *Human bodies: donation for medicine and research*, available at: <http://www.nuffieldbioethics.org/donation>.

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For example, the media have frequently heralded ‘three-parent embryos’ and ‘three-parent babies’,^{11, 12, 13} in discussing these techniques. Other commentators have compared aspects of the procedures to bone marrow donation,¹⁴ which also incorporates third-party genes into patients’ bodies in order to improve health, although these changes are not inherited by the patients’ children. Elsewhere, MST and PNT techniques have been described as being like structural repairs to functional objects, such as ‘changing the batteries in a laptop’¹⁵ or like ‘changing the bacteria in our intestines’,¹⁶ the provenance of which are not usually seen as having any resonance for social relationships.

MST and PNT would also alter the germline of the resulting child. Changing the germline means that the changes made would be passed on via the resulting person’s sperm or eggs to the generations descended from them. Based on safety and ethical concerns about germline alterations, in many countries including the UK it would be illegal to offer treatments which make such changes. It is a question for debate as to whether MST and PNT should be regarded as ethically different or acceptable in altering the germline by using mitochondria from a donor’s egg in an embryo, in the place of the mutated mitochondria that the mother would otherwise have provided.

Unlike nuclear genes, which come from both parents, only mothers can pass on their mitochondrial genes to their children. In human embryos, mitochondria are passed on from the woman’s egg because the sperm’s mitochondria degenerate as the male pronucleus forms in the fertilised egg. Therefore, while all children of a woman who has mutated mitochondria will inherit them, only her daughters will pass on the mutated mitochondria to their children and to future generations. In the same way, all children born after the use of these techniques would inherit healthy mitochondria taken from an egg donor, but only the daughters that were born could pass on copies of the donated mitochondria to their children.

¹¹ BBC News Online (5 February 2008) *Three-parent embryo formed in lab*, available at: <http://news.bbc.co.uk/1/hi/7227861.stm>.

¹² New Scientist (20 April 2011) *Three-parent babies on their way*, available at: <http://www.newscientist.com/blogs/shortsharpscience/2011/04/three-parent-babies-on-their-w.html>.

¹³ Daily Mail (12 March 2011) *Babies with THREE parents and free of genetic disease could soon be born using controversial IVF technique*, available at: <http://www.dailymail.co.uk/health/article/1365287/Babies-THREE-parents-born-years-controversial-IVF-technique-gets-ahead.html#ixzz1iaiH7YIk>.

¹⁴ BioNews (3 May 2011) *IVF and the prevention of mitochondrial DNA disease: the moral issues*, available at: http://www.bionews.org.uk/page_94023.asp.

¹⁵ The Guardian (19 April 2011) *Scientists seek to implant embryos with genetic material from three parents*, available at: <http://www.guardian.co.uk/science/2011/apr/19/scientists-embryos-three-parents>.

¹⁶ BBC News Online (26 August 2009) *Genetic advance raises IVF hopes*, available at: <http://news.bbc.co.uk/1/hi/health/8220553.stm>.

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This alteration of the germline could also mean that, if any unforeseen medical problems were to result from these techniques, they could affect not only children born via these procedures, but also their descendants. It is possible that because of the inheritance of mitochondrial genes down the maternal line, some prospective parents might request sex selection, preferring to put back only male embryos (if a choice of healthy embryos is available), based on a concern to prevent potential grandchildren's exposure to any safety risks that might be incurred by these techniques. Whether or not such medical problems eventuated, parents might also be concerned that daughters born after the use of such techniques may also face difficult reproductive decisions about whether to use their own eggs to have children. Using sex selection would not, however, limit potential health risks to the parents' own children, which is the grounds on which the procedure is usually offered. Both sexes are likely to be equally affected if problems were to be passed on alongside the healthy donated mitochondria.

Researchers have strongly recommended that families using this technique commit to allowing very long term follow-up of their children over generations, in order to further our knowledge about the outcomes of these techniques. However, this expectation may prove difficult to fulfil on the part of both families and the research community over several decades. The voluntary nature of the research relationship can make it difficult to anticipate what level of short or long-term follow up data may be able to be gathered from families.

3. The role of genetic testing

At present, some women with mutated mitochondria who would like to use their own eggs to have a baby can be offered ways to minimise, but not prevent, their risk of passing on passing mitochondrial disorders to their child. This may be done by using embryo testing techniques to gather more information about the risk of passing on health problems. They may be offered preimplantation genetic diagnosis (PGD) and/or prenatal diagnosis (PND).

Preimplantation genetic diagnosis (PGD)

Preimplantation genetic diagnosis (PGD) is a process used with IVF techniques, in which one or more cells are removed from an *in vitro* embryo for genetic testing. For women who are at risk of passing on mutated mitochondria, PGD can be used to identify which, if any, of their embryos contain the lowest level of mutated mitochondria. Using this information, women or couples may decide to go ahead with, or to avoid putting back specific embryos into the woman's womb in the hopes of beginning a pregnancy.

However, because many of the different types of mtDNA mutation are inherited in a complex and poorly-understood way, for many families PGD will not be useful because information gathered from their embryos will not permit doctors to make an accurate prognosis for any prospective child.

This can be due to the fact that - in many types of mitochondrial mutation - normal mitochondria exist in the cells alongside mutated mitochondria. The 'mutant load' (a threshold proportion of mutations in the cell beyond which the person will experience health problems) can be unpredictable and differs between individuals.

Additionally, within each individual's body, the level at which the mutant load in their cells begins to cause problems will vary for different bodily tissues. With some types of mtDNA mutations, the mutant load in cells can also change over time, making it extremely difficult to predict how severely symptoms may be experienced in future.

PGD is also not suitable for the couples who are at the greatest risk of passing on unhealthy mitochondria, where the intending mother has a particularly high proportion of mutated mitochondria ('heteroplasmy'), or where all of her mitochondria are mutated ('homoplasmy'). If all of a couple's embryos will be affected to the extent that the resulting children will have the symptoms of mitochondrial disorders, using donor eggs is currently the only way in which couples can guarantee that their children will be born unaffected.

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There are currently only a minority of MtDNA mutations for which PGD can inform a reliable diagnosis.¹⁷ These relatively few instances have specific characteristics: for example, that the severity of the disease experienced is closely linked to the level of mutant load in the cells; that the mutated mitochondria are uniformly distributed throughout the cells of the body; and that the mutant load is likely to remain at a stable level over the person's lifetime.

Prenatal diagnosis (PND)

Prenatal diagnosis (PND) is another technique which samples cells for testing in order to gather genetic information. In this case, fetal cells are taken for analysis when a woman is pregnant. As with many other prenatal tests, depending on the information that is received, some women and their partners may face a difficult decision about whether to continue the pregnancy or to request a termination.

As with PGD, because the predictive power of the information varies greatly between different types of mitochondrial mutation, only some patients are suitable for PND.

In addition to the difficulties experienced by any couple faced with a decision of whether or not to end a wanted pregnancy because of a fetal health problem, decision-making can be especially difficult in the case of mitochondrial mutations as the degree of certainty of information gained via PND may only be improved if a woman undergoes sequential testing into the third trimester (weeks 28-30),^{18, 19} by which time her pregnancy is well advanced.

PGD and PND techniques are not of use to couples who are already aware that they may be very likely to pass on a high level of mitochondrial mutations, or will pass on 100 per cent mutated mitochondria. These couples currently have no options open to them if they wish to use the woman's egg to have an unaffected baby.

Only the emerging techniques such as maternal spindle and pronuclear transfer would in theory offer women wanting to use their own gametes to have children the opportunity to prevent the transmission of mitochondrial disorders, regardless of the type of mitochondrial disorder that they are likely to pass on.

¹⁷ Bredenoord AL, Pennings G, Smeets HJ, and de Wert G (2008) Dealing with uncertainties: ethics of prenatal diagnosis and preimplantation genetic diagnosis to prevent mitochondrial disorders *Human Reproduction Update* **14**: 83-94.

¹⁸ Faivre L, Cormier-Daire V, Chrétien D *et al.* (2000) Determination of enzyme activities for prenatal diagnosis of respiratory chain deficiency *Prenatal diagnosis* **20**: 732-7

¹⁹ Steffann J, Gigarel N, Corcos J *et al.* (2007) Stability of the m.8993T→G mtDNA mutation load during human embryo-fetal development has implications for the feasibility of prenatal diagnosis in NARP syndrome *Journal of Medical Genetics* **44**: 664-9.

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How would pronuclear transfer (PNT) be done?

- First, IVF techniques are used to create an embryo using the intending parents' sperm and egg. The parents' embryo contains the mother's mutated (unhealthy) mitochondria, which came from the cytoplasm in her egg.
- At one day's development of the parents' embryo (while it is a single undivided cell)²⁰ the two pronuclei from the parents are removed from the cell for transfer. This leaves behind almost all of the mother's affected mitochondria. This enucleated cell is then discarded.
- A second embryo is created from the egg of an unrelated donor with healthy mitochondria, fertilised with sperm. If the intending father's sperm is not of sufficient quality, donor sperm would be used to avoid the need to do ICSI.²¹
- At the same very early, one-cell stage of development, the pronuclei of this embryo are removed and discarded.
- The parents' pronuclei are then placed into the second, enucleated embryo. The second embryo now contains the pronuclear DNA from the intending parents, and healthy mitochondria from the donor's egg.
- This embryo can now continue to develop and then be transferred back to the intending mother, for her to carry a pregnancy unaffected by inherited mitochondrial disorders.

About pronuclear transfer (PNT)

Scientific developments

In the 1990s, experiments^{22, 23, 24, 25} using mice had suggested the efficacy of pronuclear transfer as a means of preventing the transmission of mutated mitochondrial DNA, but the technique had not been tried in humans.

In 2003, it was reported that a research team at Sun Yat-Sen University in

²⁰ At the beginning of the process of fertilisation, the sperm and egg each contribute separate 'pronuclei' within the one-celled embryo. The genetic material in these will then merge to form the mature nucleus of the fertilised egg. From the two-cell stage of embryonic development onwards, the embryo's cells will contain one nucleus which combines both parents' DNA.

²¹ ICSI (intracytoplasmic sperm injection) is a variation of IVF in which a single sperm is injected directly into an egg to achieve fertilisation.

²² Jenuth JP, Peterson AC, Fu K, and Shoubridge EA (1996) Random genetic drift in the female germline explains the rapid segregation of mammalian mitochondrial DNA *Nature Genetics* **14**: 146-51.

²³ Meirelles FV and Smith LC (1997) Mitochondrial genotype segregation in a mouse heteroplasmic lineage produced by embryonic karyoplast transplantation *Genetics* **145**: 445-51.

²⁴ Meirelles FV and Smith LC (1998) Mitochondrial genotype segregation during preimplantation development in mouse heteroplasmic embryos *Genetics* **148**: 877-83.

²⁵ Sato A, Kono T, Nakada, K *et al.* (2005) Gene therapy for progeny of mito-mice carrying pathogenic mtDNA by nuclear transplantation *Proceedings of the National Academy of Sciences of the USA* **102**:16765-70.

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Guangzhou, China experimented with the pronuclear transfer technique in human embryos.²⁶ They transferred the embryos back to a fertility patient, which would not have been legal in the UK. Five embryos were transferred to the woman who became pregnant with triplets. The multiple pregnancy was then selectively reduced to a twin pregnancy. Some months later, the woman suffered miscarriages, losing both fetuses.

In 2008, researchers from Newcastle University in the UK told a scientific meeting that under an HFEA license granted in 2005,²⁷ they had successfully transferred pronuclear DNA between very early (day one) human embryos donated after being left over after fertility treatments. After having carried out the procedure, the Newcastle group grew ten embryos in the lab for five days before arresting their growth so that researchers could analyse them.

Although their work had not been written up in a published paper, the results were reported during debates in the House of Lords²⁸ and calls were made for the technique to be licensed by the HFEA for treatment. Media from all over the world picked up on the story, creating headlines about 'three-parent embryos'.^{29,30}

In April 2010, the Newcastle group published a paper in *Nature* reporting that human embryos developed normally to blastocyst (about 100-cell) stage in 6-8 days after pronuclear transfer providing proof of concept of the technique in human embryos in a research setting.³¹

Legal and policy developments

The Human Fertilisation and Embryology (HFE) Act 2008 (as amended) currently forbids egg, sperm or embryos which have had alterations made to their nuclear or mitochondrial DNA from being placed into a woman's body. Similarly, 'genetically modified embryos or embryos created by cloning' cannot be placed into a woman's body. However, in 2008, the Act wrote in new powers for the Secretary of State for Health to create regulations which would permit the alteration of eggs or embryos as

²⁶ BBC News Online (14 October 2003) *Foetus with three parents created*, available at: <http://news.bbc.co.uk/1/hi/health/3189718.stm>.

²⁷ HFEA press release (8 September 2005) *HFEA grants licence to Newcastle Centre at LIFE for mitochondrial research*, available at: <http://www.hfea.gov.uk/671.html>.

²⁸ House of Lords Hansard (4 February 2008) *c846*, available at: <http://www.publications.parliament.uk/pa/ld200708/ldhansrd/text/80204-0002.htm>.

²⁹ Nature News (6 February 2008) *A step towards three-parent babies?*, available at: <http://www.nature.com/news/2008/080206/full/news.2008.560.html>.

³⁰ BBC News Online (5 February 2008) *Three-parent embryo formed in lab*, available at: <http://news.bbc.co.uk/1/hi/health/7227861.stm>.

³¹ Craven L, Tuppen HA, Greggains GD *et al.* (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease *Nature* **465**: 82-5.

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part of treatment where intended to prevent mitochondrial disorders, if the technology became available and was shown to be safe.³² Both Houses of Parliament would need to support any proposed new legislation.

In February 2011, at the invitation of the Secretary of State for Health, the Human Fertilisation and Embryology Authority (HFEA) established an expert review panel to examine 'expert views on the effectiveness and safety of mitochondrial transfer'.

Their report, a '[Scientific review](#) of the safety and efficacy of methods to avoid mitochondrial disease through assisted conception' was published in April 2011. The report concluded that 'MST and PNT have the potential to be used for all patients with mtDNA disorders, which may make them preferential to PGD in the future. In patients with homoplasmy or high levels of heteroplasmy, these are the only techniques that would make it possible for them to have a genetically related unaffected child'. The report also cautioned that before MST and PNT techniques can be assessed as safe to use in treatment, specific further safety experiments need to be done before introducing them into clinical practice.

After the publication of the HFEA's scientific review, patient and medical research groups wrote a joint [letter](#) to the Secretary of State for Health about the regulation of emerging techniques to avoid transmission of mitochondrial disease. They called on Government to 'publish a timetable for the introduction of regulations so that once sufficient pre-clinical evidence is established, clinical treatment is not unduly delayed.' It is anticipated that the Government will request that further information be gathered around potential regulation of any such treatments, including public consultation, in 2012.

³² The new section 3ZA(5), in the HFE Act allows the meaning of 'permitted eggs' and 'permitted embryos' for treatment to be extended to include '*eggs or embryos that have been treated in such a way as specified in regulations to prevent the transmission of serious mitochondrial disease*'. Further provision regarding 'mitochondrial donation' is also made in section [26](#), which inserts new section 35A into the 1990 HFE Act.

How would maternal spindle transfer be done?

- First, assisted reproduction techniques are used to allow the extraction of the intending mother's egg from her ovaries. The cytoplasm of her egg contains mutated (unhealthy) mitochondria.
- Chromosomes (nuclear DNA material) in the mother's egg are found in a group which looks 'spindle shaped'. This is removed for transfer to the donor egg. The mother's chromosome-free egg containing the unhealthy mitochondria is then discarded.
- At the same time, a donated egg is taken from an unrelated woman who has healthy mitochondria.
- The chromosomes of the donor's egg are removed and discarded, leaving behind her healthy mitochondria in the cytoplasm.
- The 'spindle' of chromosomes taken from the mother's egg is now placed into the enucleated donor egg.
- The resulting reconstructed egg contains nuclear DNA from the mother, and healthy mitochondria from the donor.
- This egg can then be fertilised with sperm from the intending father, and the resulting embryo transferred back to the intending mother. This will enable her to carry a pregnancy that will be unaffected by inherited mitochondrial disorders.

About maternal spindle transfer

Scientific developments

Maternal spindle transfer is a similar technique to pronuclear transfer, the main difference being that it uses unfertilised eggs instead of early embryos.

In 2009, researchers in Oregon announced they had successfully used maternal spindle transfer in rhesus macaques.³³ They found the primate eggs capable of supporting normal fertilisation, and went on to have normal embryo development. Three healthy offspring were produced. No mutated mitochondria from the affected egg were detected in the three monkeys born. Their growth is monitored monthly and, thus far, at the current age of over two years, no difference has been noted between the experimental macaques born following maternal spindle transfer and controls.

In collaboration with the researchers from Oregon, researchers at Newcastle University are currently testing the maternal spindle transfer technique on human eggs, the results of which have yet to be published.

³³ Tachibana M, Sparman M, Sritanaudomchai H *et al.* (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells *Nature* **461**: 367-72.

Legal and policy developments

The same legal and regulatory constraints currently apply to the maternal spindle transfer technique in the HFE Act 2008, as to the pronuclear transfer technique. Similarly, maternal spindle transfer would be permitted for use in treatment only if Parliament agrees that the meaning of 'permitted eggs' for treatment should be extended to include '*eggs...that have been treated in such a way as specified in regulations to prevent the transmission of serious mitochondrial disease*'.