Mitochondrial DNA disorders – is there a way to prevent transmission?

Summary of how the HFEA made its decision to licence this project of research

1. As required under the HF&E Act 1990 the HFEA's Licence Committees make all decisions about HFEA licences, where appropriate seeking external advice. Each Committee is made up of five Authority Members who determine whether a licence should be granted, suspended, varied or revoked.

2. The HFEA received an application from Dr Mary Herbert, Newcastle Fertility Centre at LIFE, in May 2004 to study methods to prevent the transmission of mitochondrial DNA disorders.

3. This application was considered by the HFEA's Research Licence Committee at its meeting on 15 September 2004. The Research Licence Committee was made up of Authority members with a lay majority and a lay chair. The Committee also had access to additional legal, scientific and clinical expertise to support its decision making.

4. In considering whether to grant a licence, the Committee considered the following documentation:
   - Application form signed by the Person Responsible and the Nominal Licensee
   - *Curricula vitae* of the principal personnel involved in the research
   - Approval of a properly constituted local research Ethics Committee
   - Report of the HFEA inspection of the research centre that occurred on 27 May 2004
   - Opinions from 2 peer reviewers, selected by the HFEA
   - The Centre's licensing history
   - Patient Information and Consent Forms, submitted by the Centre

5. The Committee considered, in accordance its statutory obligations under the HF&E Act 1990, whether any of the activities in the proposed project of research were prohibited under the HF&E Act 1990.

6. The Committee, after careful consideration, refused to grant a research licence as it agreed that the proposed research activities were prohibited under paragraph 3(4) of Schedule 2 to the HF&E Act 1990.

7. The Centre decided to make representations in relation to the Licence Committee's decision to refuse to grant a research licence. These

representations were made to the Research Licence Committee at its meeting on 24 November 2004. The Committee considered written and oral representations made on behalf of the Centre.

8. The Committee, again after careful consideration, decided to uphold its original decision and refused to grant a research licence.

9. The Centre decided to appeal against this decision. The appeal was heard by an HFEA Appeal Committee, in accordance with the HF&E (Licence Committees and Appeals) Regulations 1991, at a meeting on 1 September 2005.

10. The Appeal Committee heard oral submissions on behalf of the Centre and the Licence Committee (which were both legally represented) and had the benefit of oral evidence from Professor Turnbull and Professor Burns. The Appeal Committee was further assisted by an expert, Professor Mary Sellar who attended and gave evidence to assist the Appeal Committee on the scientific questions which arose in the course of the Appeal. The Appeal Committee also had an external legal advisor at the hearing. New material and issues were advanced during the hearing which contributed to the Appeal Committee's deliberations.

11. The Appeal Committee approached its decision in a sequence of steps to be determined. The first issue was whether any of the activities within the proposed research were prohibited by the Act:

    Section 3(3)(d) of the Human Fertilisation and Embryology Act 1990 provides: "*A licence cannot authorise replacing a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo*"

    Schedule 2 Paragraph 3(4) of the Human Fertilisation and Embryology Act 1990 provides: "*A licence under this paragraph cannot authorise altering the genetic structure of any cell while it forms part of an embryo, except in such circumstances (if any) as may be specified in or determined in pursuance of regulations*"

12. The Appeal Committee considered that the research was not prohibited by the provisions of either Section 3(3)(d) or Paragraph of 3(4) of Schedule 2.

13. In relation to Section 3(3)(d) of the HF&E Act the Appeal Committee's reasons were as follows:

- The Appeal Committee noted that the proposed research would involve the removal of the pronuclei at the one cell (zygote) stage and transfer of the pronuclei into another enucleated zygote. The Committee accepted the view that: "*the zygote … at no stage contains a single nucleus. First it has two haploid pronuclei, then two diploid pronuclei, and then it enters mitosis. There is no diploid nucleus, with a complete complement of chromosomes until we reach the two-cell stage" "one-celled embryos … do not contain single diploid nuclei*"

- The Appeal Committee was satisfied that the pronucleus is not the same as the nucleus and, having reached agreement on this distinction, considered that the prohibition contained in section 3(3)(d) of the Act did not extend to the proposed research involving the pronuclei.

14. The Appeal Committee next went on to consider paragraph 3(4) of Schedule 2 to the HF&E Act 1990. The Appeal Committee focussed first on the meaning to be applied to the words "genetic structure". The Appeal Committee considered that there is ambiguity in the wording used in this paragraph of Schedule 2; it felt the words "genetic structure" were ambiguous, a proposition not contested on behalf of the Research Licence Committee, and it accepted the evidence that there was no accepted or standard definition of the phrase within the scientific community. The meaning to be given to these words was a central issue with which the Appeal Committee had had to struggle during their consideration of this case. The Appeal Committee considered it to be their task to interpret the phrase "altering the genetic structure of any cell" within the context of the paragraph and the Act, so as to determine the issue of any statutory prohibition to the proposed research.

15. Given the ambiguity of the words used in the statute the Appeal Committee sought to use a number of interpretative criteria to assist them to identify the true meaning of the enactment.

16. The Appeal Committee accepted the view of the scientific community, as expressed in the evidence presented to them, that when pressed to give meaning to the phrase, it considered "genetic structure" to have a relatively narrow definition. Such a definition would centre on the expression of nuclear genes that result in heritable characteristics.

17. Furthermore the Appeal Committee felt that a common sense or plain meaning of the words in Paragraph 3(4) should be derived from the usual meaning given by a lay person in relation to the word "genetic" which would include the expectation that an "alteration to the genetic

structure" would involve alteration to the genes or the genome and the resulting heritable characteristics.

18. In the Appeal Committee's view, adopting what might be considered a narrow definition of this term is aligned with the purposive intent of the parliamentarians involved in the passing of the Act. Having considered carefully the pre-enactment history and in particular the White Paper, the Appeal Committee was satisfied that the Parliamentary concern in relation to this area had been to restrict techniques which would allow the artificial creation of human beings with certain pre-determined characteristics through modification of an early embryo's genetic structure. (See paragraph 37 of the White Paper). The Appeal Committee did not accept that paragraph 3(4) of Schedule 2 derived from matters set out in paragraph 36 of the White Paper.

19. The Appeal Committee went on to apply its interpretation as to the meaning of altering the genetic structure of the cell, to the various activities envisaged within proposed research.

20. The Appeal Committee accepted that Mitochondrial DNA is not associated with identity or any pre-determined characteristics of the individual. The Appeal Committee considered that the process of removing the pronuclei from the zygote does not cause the genetic structure to be altered, nor does the depositing of the pronuclei in the cytoplasm of an enucleated zygote (which it is recognised contains Mitochondrial DNA). The Appeal Committee was satisfied that where pronuclear material is deposited into a new cell this does not change the genetic structure of the new cell because the nuclear material over-rides any DNA in the mitochondrial DNA.

21. The Appeal Committee went on to consider the meaning to be attributed to the more extended phrase "altering the genetic structure of any cell while it forms part of an embryo". The Appeal Committee accepted the advice of its Legal Adviser that for these purposes "embryo" must be given the definition as set out in section 1 of the HF&E Act 1990:

> "*Embryo means a live human embryo where fertilisation is complete and references to an embryo include an egg in the process of fertilisation*".

22. However, even applying this definition, the Appeal Committee was satisfied that once the pronuclei had been removed from a cell it no longer constituted an embryo. Whilst accepting that the process of removing the pronuclei does change genetic **constitution or composition** of the cell (or embryo as defined by the Act) the Appeal

Committee did not consider this activity alters the genetic **structure** (the definition of structure having been discussed above).

23. The Appeal Committee was also satisfied that the enucleated recipient cell into which the pronuclei are to be inserted under the proposed research, is not an embryo (however defined).

24. Having dealt with the interpretation of the phrase in this way the Appeal Committee did not consider it necessary to deal with arguments as to whether a cell of a single cell embryo could be said to be “part of” the embryo.

25. Overall the Appeal Committee was satisfied that none of the activities in the proposed research involve altering the genetic structure of any cell while it forms part of an embryo.

26. The Appeal Committee had borne in mind, throughout its interpretative exercise the overall intention of Parliament which it believed was to address the mischief of altering the genetic structure with the intention of selecting characteristics, or ensuring a predisposition as to certain characteristics, of the potential human being. The Appeal Committee had regard to all the material and submissions in relation to interpretation and was particularly assisted by the correspondence from Dr Anne McLaren who had been a member of the Warnock Committee.

27. The Appeal Committee had regard to the very recent publications (August 2005) of the “Review of the Human Fertilisation and Embryology Act” and “The Government Response to the Report from the House of Commons Science and Technology Committee”. Having considered both documents the Appeal Committee welcomed the Government proposal to consult on amending the law in this area, and the Appeal Committee would welcome further clarification in what is clearly a difficult area.

28. Having concluded that none of the proposed activities are prohibited under the Act the Appeal Committee went on to consider the other issues relevant to the issue of a Research Licence. In doing so it reviewed the material which had previously been available to the Research Licence Committee including the original application and the comments of the Peer Reviewers.

29. The Appeal Committee considered that the proposed activities were necessary or desirable for one of the specified purposes in the Act, namely:

- to increase knowledge about serious disease [paragraph 2(2)(b) of the Human Fertilisation and Embryology (Research Purposes) Regulations 2001]; and
- to enable any such knowledge to be applied in developing treatments for serious disease [paragraph 2(2)(c) of the Human Fertilisation and Embryology (Research Purposes) Regulations 2001] .

30. The Appeal Committee was satisfied that the proposed use of embryos is necessary for the purpose of the research.

31. The Appeal Committee was satisfied with the Patient Information. The Appeal Committee understood that the Consent form for this research would be in the same form as the consent form currently used at the Centre for other research projects. They understood that it has been considered and approved in relation to other research licences which have been granted to the Centre.

32. The Appeal Committee considered that it was appropriate to grant a Licence for research in this case. The Licence should be subject to the statutory and standard conditions for licences as set out in the Act and the current Code of Practice. Additionally, since this is a very new area of research using techniques which have been the subject of careful consideration during the course of the Licensing process, a condition should be attached to the Licence requiring the Centre to provide progress reports to the Authority every six months.

33. The Appeal Committee was satisfied that the Nominal Licensee (Professor Alison Murdoch) is a suitable person to hold a Licence and that the character, qualifications and experience of the proposed Person Responsible (Dr Mary Herbert) are such as are required for the supervision of the activities and that she will discharge her duty under section 17 of the Act.

34. On the basis of the satisfactory Licensing history the Appeal Committee was satisfied that the premises in respect of which the Licence is to be granted are suitable for the activities proposed.