Submission to Inquiry into Mitochondrial Donation

Introduction.

This submission seeks to draw the Committee's attention to some issues arising from proposals for the incorporation of mitochondria from a woman, other than the intended mother, into an embryo generated by the combination of nuclei of gametes from the mother and the father. The submission has been condensed where possible with few references, however if any Committee member requests information regarding sources of any specific issue raised in it these can be provided.

A brief summary of relevant biology.

Almost every cell in a mammalian body contains many small entities, termed mitochondria, within its cytoplasm. Whilst the overwhelming number of an individual's genes are located in the nucleus of each cell in that individual's body, the DNA in which a very small number of genes is encoded is located not inside a cell's nucleus but in mitochondria in the surrounding cytoplasm.

Spermatozoa travel very light and contain little more than the nucleus bearing the male's genome. Specifically, they completely lack any mitochondria. Consequently, following the fertilisation of an ovum (oocyte) by a sperm, all of the mitochondria incorporated in the resulting embryo have been derived exclusively from the oocyte donor (commonly referred to as the mother). That fraction of the genome of any embryo, fetus or child represented by mitochondrial DNA is always derived exclusively from the mother, grandmother, great grandmother etc. etc. The male parent from any generation does not get a look in.

Notwithstanding the numerically small contribution which mitochondrial DNA makes to the genome, this mitochondria (mt) DNA is essential for cellular function and any perturbation of that function, for example by a mutation affecting mtDNA can have a major impact on an individual's health, in the form of interference with, or aberration of, normal function of a variety of organ systems in the human body. Some of the issues raised by mitochondrial transplantation as a means of reducing the risk to offspring of maternally transmitted diseases will be identified in this submission.

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1. The regulation of mitochondrial transplantation in the United Kingdom.

***Those who cannot remember the past are condemned to repeat it. (S*antayana)**

Any Australian initiative to follow the UK legislation would be well advised to consider possible consequences of that legislation carefully (George Santayana knew a thing or two)

The introduction, in 2014/5 of legislation into the UK Parliament to confer on the Human Fertilisation and Embryology Authority (HFEA) the power to regulate experimentation with, and potentially the clinical practice of, mitochondrial transplantation in the course of the creation of human embryos, set an international precedent. The legislation represented the first instance in which a universally accepted precept, namely that alteration of the human genome was off limits, was formally discarded by any government. I am not aware of any other jurisdiction which has legislated to follow the UK. Given the history of unregulated operators in the field of unauthorized experimentation relating to human reproduction, it's difficult to exclude instances of procedures endorsed in the UK legislation being underway in any other location.

. Following the passage of the bill through the Commons in late 2014, it was introduced into the House of Lords in 2015 in order to debate an amendment. This was intended to defer its final approval in order to allow more detailed consideration of safety issues raised by the legislation. Issues of risk raised in that amendment, which was unsuccessful, nevertheless remain substantially unresolved and serve to highlight concerns which remain extremely relevant if another legislature considers the possibility of following the UK lead. These issues will be identified in this section dealing with the UK legislation but will also be considered in subsequent sections. Those sections will also draw attention to other issues which the writer considers to be relevant to the Senate Committee's deliberations although not identified during the UK debate.

When introducing the bill into the Lords, Earl Howe summarised its intent as: *to enable women to have their own genetic children, free of terrible disease caused by disorders in their mitochondrial DNA. The regulations do so by allowing healthy mitochondria from a donor to replace the unhealthy mitochondria in a woman's egg or embryo.*

The amendment to be debated, proposed by Lord Debben, was that new draft regulations not be introduced until a joint committee of both Houses was established and reported on:

(1) the safety of the procedures permitted by the draft regulations,

(2) the compliance of the draft regulations with European Union and domestic law, and

(3) the key definitions used in the draft regulations

Several amendments which might have constrained implementation of the *proposed* **legislation were considered but not adopted. The first of these related to the welfare of four categories of individuals who would be affected by mitochondrial transplantation. These were the woman who was to provide oocytes as a source of normal mitochondria, the woman whose oocyte or embryo was to be the mitochondrial recipient, the recipient embryo (and subsequent child) arising as a result of this procedure and any future generations derived from the progeny of that child, if she was female, when she attained adult life.**

The second proposed amendment related to a prohibition in a European Charter, and the extent to which UK law complied with this. The modification of the human genome in the course of medical practice was specifically prohibited in the Charter. This prohibition in the Charter expressed a longstanding consensus dating to the early days of clinical genetics.

The third proposition reflected the burgeoning vocabulary included in the legislation and a concern that the precise connotations placed on novel technical terminology should be universally agreed before deciding to enshrine this in legislation.

Of relevance to the Australian Senate, in discussion of possible benefits and risks attaching to the various categories of participants, it was observed that: ***legislators have to consider not just individual interests but the interests of our society more broadly and should consider too what precedents are set and what lines are crossed by the laws and regulations we make.***

The response to queries from the noble Lords about the extent to which the HFEA had presented results of its research insofar as they related to possible benefits and risks of mitochondrial transplantation was that: ***the evidence was verbally produced. The reason why it is not published is that anything that is published, even in the form of an extract, cannot then be published in a reputable journal..*** **With respect, one expects that any responsible assembly of legislators in this century should have had the wit to recognise that acceptance by, and publication in, a peer reviewed journal**

is mandatory before accepting scientific data, career interests of the author notwithstanding.

The phrase 'mitochondrial donation' bit the dust in the course of the Lords debate: ***because Newcastle is not offering to provide donation opportunities for women but is asking them whether they will sell their eggs, at £500 per cycle.***

In response to a question of whether genome modification occurs in the course of mitochondrial transplantation, it was asserted that: ***The reason it is not genetic modification, as the term is understood by most people, is simple: this is therapeutic, not eugenic.*** **In anticipation of examining the issue of whether mitochondrial transplantation is effectively genome modification, it should be made clear that any answer to this question should be determined, irrespective of what most people understand, by the nature of what mitochondrial transplantation actually entails. Whilst this issue was quietly shelved at that time, it received more consideration in the 2020 House of Lords debate (see below).**

Dependent on the specific circumstances, the procedure of modification of the human genome may be undertaken to attain eugenic, therapeutic or experimental goals however the ***biological nature*** **of the procedure will be the same in each case. Regardless of the declared intention, if it walks like a duck and it quacks then . . .**

Some informed comments on the impact on a family of the birth of a severely disabled child were provided during the debate by Baroness Hollis, a psychiatrist with over 30 years experience of working with families of severely disabled children and herself the mother of a child with a severe developmental disability: ***My heart goes out to those parents facing the prospect of inherited mitochondrial disorders. As a mother, I understand what is called the moral imperative to try to help. However, our first responsibility must be to the children who may be created through these proposed interventions: the most important moral imperative must be to do no harm. A new technology of such potential importance must take as long as is needed to be as sure as possible of its safety. Being first is not always best.***

Whilst the question of whether the European restriction on undertaking genetic modification extended to UK law need not be an issue for the Australian Senate it is of interest that both the then current and two preceding UK Attorneys-General all voted against the bill. This was interpreted as an indication that they believed it to be contrary to UK law to the extent that this was compliant with the European Charter prohibition of human genome alteration.

The extent of concerns that the introduction of human mitochondrial transplantation (especially with minimal prior experimentation in appropriate non-human species models in which the risks of disease in subsequent generations could

be modeled) was acknowledged in paragraph 3.7.29 of the HFEA expert panel report:

Until knowledge has built up that suggests otherwise, any female born following maternal spindle transfer or pronuclear transfer (MST or PNT), should be advised, when old enough, that she may herself be at risk of having a child with a significant level of mutant mtDNA, putting her child and, if female, subsequent generations at risk of mitochondrial disease.

MST and PNT are alternative techniques to accomplish mitochondrial transfer. The UK legislation permitted the trialling of both in clinical practice on the basis that different laboratories were using different approaches. A fundamental ethical distinction between them failed to attract comment but will be examined below.

2. Second House of Lords Debate

In January 2020, the House of Lords returned to the subject of gene editing in response to a motion to the effect that the House takes note of recent developments in the field of gene editing. This session took the form of a series of observations. What follows represents a summary of points raised into human gene editing (these were accompanied by other observations relating to editing in horticulture).

Attention was drawn to an article in the journal Nature in August, 2017. In this, George Annas, Director of the Center for Health Law, Ethics and Human Rights at Boston University of Public Health asserted, when discussing human gene editing, that "the scientists are out of control".

Lord Winston, who had been prominent in the field of developing human IVF, urged their Lordships *to consider the wider issues that are at stake here.*

A statement from the British Society for Genetic Medicine included in comments on the earlier legislation concluded that "such a venture therefore needs to be fully researched and the ethical and social aspects require careful consideration before roll-out in the general population". This statement was brought to the attention of the House by Lord Winston.

Reference was made to a 2019 article in the journal Nature. In that article a group of 18 scientists and ethicists from 7 different countries called for:

"a global moratorium on all human genome editing – that is changing heritable DNA in sperm, eggs or embryos to make genetically modified children. That future generations could have permanent, and possibly harmful, effects on the species".

Another claim was presented to the effect that "germ line editing is not yet safe or effective enough to justify any use in the clinic".

A statement from Emmanuelle Charpentier, co-inventor of CRISPR technology, that "uncertainty would probably remain even with experience, study and future research" was noted.

The point was made that around 30 countries have legislation which directly or indirectly bans all clinical uses of germ line editing.

It was brought to the attention of the House that Australia, Canada, Germany, Israel, Switzerland and the Netherlands prohibit human germ line gene therapy. The techniques were said to be unsafe. It was asserted that there is insufficient knowledge of the risks to future generations.

Finally, it was noted that the European Court of Justice has ruled that all genome edited organisms should be regarded as genetically modified.

Ethical consequences of the clinical introduction of mitochondrial replacement techniques

Numerous responses to the authorisation of the new techniques appeared in the following year, generally expressing concern about risks inherent in it. These concerns have prompted proposals for addressing further ethical questions.

The issue of how genome modification , undertaken for medical reasons, is to be assessed was identified by a specialist from the Great Ormond Street Hospital for Children, recognised as one of the pre-eminent British institutions responsible for care of children afflicted by the group of inherited conditions the prevention of which is likely to be the target of attempts at mitochondrial transplantation*:*

Ultimately, decisions about what we should do with gene editing must be determined by reference to other non-genomic texts that determine what it is to be human - rather than simply to undertake gene editing because it can be done.

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Emphasising the possible long term adverse effects of genetic modification following mitochondrial transplantation, one British scientist, Christopher Exley referred to: ***a genetic experiment which could have disastrous consequences for generations***.

John Appleby from the Centre of Medical Law and Ethics at Kings College, London responded to the UK legislation also emphasising the potential for harm from use of the newly authorised procedures: ***The ethics debate should now be re-oriented***

towards recommending ways that regulators and clinicians can reduce or eliminate the possible health risks of the first clinical use of mitochondrial transplantation .

Alternative attitudes in relation to the clinical adoption of mitochondrial transplantation in order to avoid potential harm to children born after the use of this procedure have been expressed especially by those undertaking research on this with a view to its clinical introduction. Examples include: *Of course we were focused on the science, not the ethics.* (Professor Lovell Badge addressing the House of Commons Science and Technology Committee, 22/10/2014).

Later in the same hearing, the Professor asserted, in response to suggestions that the technology should first be tested in macaques: *The only species you can do this research on is humans.* A similar conviction to exclude monkeys as subjects was repeated two years later in the course of the fourth HFEA Scientific Review of the safety and efficacy of methods to avoid mitochondrial disease: *Pronuclear Transfer (PNT) in a non-human primate model with the demonstration that the offspring produced are normal is not critical or mandatory.*

Other indications of the construction placed on this form of genetic manipulation and, in particular, on its legal implications have included questions as to whether mitochondrial donors should incur parental responsibilities for any children created and whether donation could be anonymous, in contrast with the British requirement for disclosure of the identity of gamete donors.

Further tacit recognition of the genetic modification nature of mitochondrial transplantation has been acknowledged by advocacy for use of this technology to be linked to a requirement for sex selection in relation to the generation of children using this technology. Unless only males are selected, it is argued, the condition coded for by the abnormal mitochondrial DNA may reappear in a future generation. As noted above, the male parent does not contribute to the mitochondria of offspring.

To ensure that the mutated DNA is not transmitted to any children leading to a risk of transgenerational impacts, it has been proposed that licences to undertake mitochondrial transplantation should be restricted to British clinics which commit to gender selection for males. There have been warnings that, even if the first generation of females is not clinically affected, mitochondrial coded disease may nevertheless emerge in later ones. Birth of a clinically normal infant may not necessarily guarantee similar normality in the following generation.

4 Alternative technical approaches to provide oocyte cytoplasm containing normal (non-mutated) mitochondrial DNA.

Two alternative approaches exist to the elimination of cytoplasm containing mutated mitochondria from an oocyte of the intended mother and its replacement with the cytoplasm of an oocyte from another woman free from mitochondrial mutations before undertaking its fertilisation with spermatozoa from the intended father.

In one approach, maternal spindle transfer (MST), the 'maternal spindle' (the spindle shaped group of chromosomes containing the mother's nuclear DNA) is removed from one of her oocytes and transferred to an unfertilised oocyte from another woman, free of mitochondrial mutations, which has had its own DNA-containing nuclear spindle removed. This composite oocyte is then fertilised by spermatozoa from the intended father.

In the other approach, pro-nuclear transfer (PNT), ***the pronuclei (nuclear material)*** **is removed** ***from a newly fertilized*** **(with paternal spermatozoa)** ***egg that has unhealthy mitochondria. The pro-nuclei are then transferred to a donated embryo, with healthy mitochondria that has had its own, original pro-nuclei removed*** **(text in italics is extracted from para 7.3 of the Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015). The term 'pro-nucleus' refers to the nucleus of a spermatozoon or oocyte during the process of fertilization prior to their fusion.**

It has been asserted by some biologists, on the basis of research in nonhuman species, that the extent to which an individual's (maternally derived) mitochondrial genes correspond with nuclear (paternally derived) genes is likely to influence the extent to which any mutant mitochondrial genes will be expressed as disease. Clinicians have frequently disputed this possibility, however if it were to be even partially accurate, it would point to the requirement for efforts to match the recipient (donor) oocyte's mitochondrial DNA with maternal haplotype nuclear genes.

Heteroplasmy and Mosaicism – Their Significance

The frequent occurrence of the two phenomena in this heading, can considerably interfere with, estimation of both the uniformity among an oocyte's mitochondrial genes and its consistency throughout the different tissues of an individual generated from that oocyte.

The term'heteroplasmy' refers to the presence of two variants of mtDNA (normal and 'disease generating') mitochondria within a single cell. Mosaicism describes the situation in which different cells comprising an organ contain differing ratios of normal and abnormal mtDNA within their cytoplasm. Both constitute serious obstacles (which may potentially be inescapable) to an accurate assessment of the

extent of abnormal mtDNA in any cell and also to the percentage of cells in any organ likely to be affected by any degree of heteroplasmy.

The complexity introduced into management of mitochondrial mutation by these factors was summarised in Appleby's article above:

Heteroplasmic mtDNA mutations (e.g. neurogenic muscle weakness, ataxia, retinis pigmentosa, or NARP) are among the most common and while these mutation(s) will always be inherited by offspring, the mutation loads that are present in those offspring will often vary from person to person and depend on their age. The variability of mutant loads among heteroplasmic mtDNA mutants carriers is the result of mosaicism in the developing embryo, which is caused by genetic bottlenecks during mitochondrial division.

In the absence of any means readily to obtain some reliable assessment of this information, any accurate assessment of the risk or the severity of future mitochondrial generated disease in an embryo is not feasible. There has been a reported case of a 7 month old male infant produced by the technique of 'spindle transfer' described above. Testing of the load of mutant mtDNA in his cells collected from a variety of tissues from his body revealed a range of 2.36% to 9.23%. The clinicians reporting the case (Kang *et al.*) cautioned that: *the boy is currently healthy at 7 months of age, although long-term follow-up of the child's longitudinal development remains crucial.*

It is appropriate to caution that cytoplasmic transfer to recipient oocytes has been tested intermittently since the 1990s as a means of treating infertility of uncertain origin. The occurrence of cases of major developmental abnormalities in children resulting from this technique has led to curtailment of its more recent use.

Other examples of Transgenerational Exercise of Parental Autonomy

I've listened to all this. I want to have my own baby and I'm going to take the chance **(oral evidence given by Professor Turnbull to the House of Commons Science and Technology Committee). The comments alluded to the response of some patients to genetic counselling and explanation of all options.**

Both the extent and the legitimacy of parental decision making in relation to children, especially in situations in which the parent makes the choice and the child takes the risk, have attracted more attention over the last two decades than at any previous time. The issue which has evoked this attention has, of course, been that of vaccination. Following a single flawed report in a major medical journal proposing

that vaccination could increase the risk that a child would subsequently develop autism, a vigorous 'anti-vaxxer' movement rapidly emerged.

Subsequent refutation of this completely invalid proposition by numerous credible medical practitioners failed to deter the anti-vaxxers who commonly were from among the (supposedly) better educated community members.

The decision to withhold vaccination from children made, on their behalf, entirely by their parents, can impose significant adverse consequences on affected children. Not only are the non-vaccinated children placed at a significantly heightened risk of several infectious diseases, but their persisting susceptibility and liability to function as carriers inevitably increases the potential exposure and risk of other children to the micro-organisms responsible for these conditions.

Paradoxically, other legislated constraints on parental autonomy in relation to the safety of their children are well entrenched. Many of these relate to children in motor vehicles. Examples include use of appropriate restraint, avoidance of cigarette smoking in a car with a child passenger and, most egregiously, confining a child in a non-attended vehicle.

In the light of existing and accepted constraints on parental autonomy in relation to decision making on issues such as these, it is rather surprising that impacts of its unfettered application on potential children and *their* children in relation to mitochondrial transplantation appear not to have attracted comparable attention.

An awareness of a strong possibility that a couple will produce a child with a major disability has traditionally resulted in a decision to avoid pregnancy. Since the 1980s, IVF related technologies, developed initially as a response to infertility, have offered an increasing range of possibilities for safer pregnancy options for couples when one member introduces a risk of a major genetically transmitted abnormality.

Examples of such strategies include the use of donor gametes (ovum and/or spermatozoa) in an IVF conception. In considering this option, a report to the House of Commons Science and Technology Committee (22/10/2014) reported that: ***it is within our means to offer aspiring parents better options than those requiring the patient(s) to use an egg donor (when the latest HFEA figures confirm that there remains a national shortage of donors).***

The report supported the use of mitochondrial transplantation on the basis that it would be unethical not to offer aspiring parents better options than these. Perhaps surprisingly, this report seemed not to note that the national shortage would impact similarly on procurement of oocytes to be used as a source of cytoplasm in replacing maternal mitochondria. It might be reasonable to rank the applicable imperatives generated by not having any child versus not being able to have a child who inherited the maternal genotype.

In instances of infertility, the intrauterine introduction of a donated embryo, unrelated to either parent, may be undertaken. Several decades of widespread use have established a high probability both of safety and of success for such procedures.

It is, perhaps, rather surprising that discussion of new technologies in the Lords debate concentrated exclusively on the practicalities, in particular the relative likelihood of success, reflected in the birth of a healthy, preferably male, child following the use of two alternative approaches. Any mention of possible ethical, as distinct from practical, questions was lacking, even in contributions from mitred members of the Lords. Given that one of the competing strategies (PNT) entails the creation of an embryo with the specific purpose of then dismantling it to provide the requisite microenvironment for a new embryo whose nuclear DNA will be derived exclusively from the parents entered into the program, this omission is quite disturbing.

No general agreement exists about the status of the human embryo in relation to personhood. Philosophers will no doubt continue to find material for writing on this. Nevertheless I submit, as noted above by the clinician from Great Ormond St Hospital, the separate question about *humanness* can and should be addressed, irrespective of one's views on personhood.

First, do no harm. An embryo, including one generated with the intention of using it as a source of spare parts, irrespective of the outcome which is sought from such use, effectively crosses a line which potentially establishes a precedent with possibly unlimited future use.

A precedent may remain unrecognised for years. Its application in innovative situations may not become apparent for decades. To some extent, the basic issue which those advocating the production of embryos with the specific intent of then dismantling them refrain from addressing is not whether an embryo is entitled to respect because it is a person. The fundamental issue surely is that, biologically, it is unequivocally a *human entity*. The precedent, the setting of which may be imminent, is that *use* of a biologically human entity as a sequel to its generation with that use in mind crosses a major threshold. Threshold crossing may not commonly entail rapid major opportunistic response. More frequently, a sequence of relatively minor 'bracket creeps' occurs (Santayana again).

I remain unaware of any controlled studies which have sought to estimate the extent to which the delivery of a child who is genetically related to only one of its postnatal parents (in the case of mitochondrial transplantation its father) or to neither of these, impairs a couple's appreciation of, love for or caring response to, the child. Unfortunately, parental disregard for, or neglect of, a child is not unknown in contemporary society but I would seriously question whether this is more likely to be a feature of families in which a child is genetically related to only one, or to

neither of the birth parents. I'm unaware of whether studies have been completed to compare the impact of genetic relationship of a child either to only one, or to neither of the parents taking it home from the maternity ward, on the value placed on the child by those parents. There could be a PhD in that one.

Finally, addressing the relevance of these existing, well developed techniques for couples in whom the woman is known to carry a mitochondrial mutation imposing major risks on any progeny, it is appropriate to consider briefly what it is that a couple envisages as the most rewarding outcome of producing a child. Traditionally, I suggest, it is likely to be the fulfilment of a wish to have a baby to whom love can be extended, and reciprocated, in day to day caring and throughout growth and development. Before the emergence of contemporary reproductive technology, the only available option, adoption, appears generally to have been as successful as 'conventional' child production. Failures occur in both situations but greatly outnumbered by successes.

3. NHMRC Scientific Statement.

The NHMRC Mitochondrial Expert Committee report included a Working Committee Statement. It was indicated at the outset that there was considerable diversity among the committee in relation to some questions. There was reference to robust discussion and diversity of viewpoints. Nevertheless the resulting statement was at pains to represent a range of views in the best traditions of scientific inquiry.

The first question to be addressed was that of whether mitochondrial donation is distinct from germ line genetic modification. Applying some flexible linguistics, it was acknowledged that it was essential to recognize the potential heritability of changes to the genome as a result of mitochondrial donation". The duck analogy raised earlier in this submission comes to mind.

The second question asked whether there was any new information from research findings in the UK that the science of mitochondrial donation is safe for introduction into controlled clinical practice in an Australian context. It was concluded that there was no significant evidence since the 2016 HFEA review about the safety and efficacy of mitochondrial donation. There was complete consensus in relation to this.

The third question considered whether other approaches to the problem of inherited mitochondrial disease should also be the focus of Australian research. There was a

diversity of responses. One recognises that any reviewing group charged with providing an answer to a question relating to a parliamentary inquiry is constrained to responding only within the terms of that inquiry. On the other hand, as a generally applicable principle, it's a safe bet that, if one doesn't address a question, one is unlikely to find an answer to it. It was concluded, in passing, that there was currently no known cure and that treatment options were limited largely to management of symptoms.

The terms of the committee's inquiry were confined to the means of control of mitochondrial based diseases both in the patient and in any progeny. As acknowledged, the latter goal entailed genome modification by means of mitochondrial transfer. Had this constraint to inquiry not existed it could have been appropriate to consider the current state of research concerned with the use of mitochondria to ameliorate the effects of deleterious mitochondrial mutations in an existing patient. The status of that research approach will be briefly considered in section 4.

4.Alternative Scientific Approaches

The intention of the legislation which prompted this Committee inquiry was specifically to enable the development of mitochondrial transplantation as a means of preventing the intergenerational transmission of disease. This was a consequence of the fertilisation of oocytes carrying deleterious mitochondrial mutations. The effect of successfully preventing fertilisation of affected oocytes should be the prevention of new cases of disease produced by mitochondria carrying mutations.

Investigation of this problem in the course of the Senate inquiry to this point has revealed very clearly that research has progressed very slowly since constraints were removed in the UK. It appears likely that therapeutic measures which are safe, effective and ethically acceptable to all involved are unlikely to be forthcoming for a prolonged period. Were one to look more widely than the precise goal enshrined in the relevant bill it would not be too difficult to consider alternative solutions which could well be available in a much shorter timescale and could also carry fewer risks. Directing attention to these, at least in the short to medium term, need not exclude ongoing examination of possibilities for interrupting intergenerational transmission of mitochondrial disease.

I appreciate that those responsible for initiating this legislation are committed to there being but one solution, namely that encompassed in the bill. Whilst that may be the way in which politicians think, it is certainly not the way in which scientific progress has been achieved. When one has a problem, I submit that the scientist's response entails, in the first instance, dissecting it into its components and then addressing possible approaches to resolving them individually.

Adopting such a scientific response to the challenge posed by disease conditions attributable to mitochondrial mutations, it hardly requires extraordinary perspicacity to identify two potential research pathways. These are firstly prevention of intergenerational transmission and secondly the treatment of an existing condition. The proposed legislation has been committed to the first while reports of inquiry into its implementation have disparaged the second. With respect, I submit that any scientific review would identify the second as much more likely to be achievable than the first path..

While drafters of the legislation might assert that prevention of transmission is the be all and end all, the manner in which the proposed legislation has been presented to the Australian community suggests otherwise. The naming of the bill and its identification with an unfortunate child who has no chance of benefitting in any way from implementation of the only line of research under consideration, irrespective of the speed of its approval, suggests that its proponents foresee mileage in this approach (my apologies for not devising a metric equivalent to mileage). I intend to make further reference to the nomenclature of the bill below.

It is incontestable that there will be a significant number of unfortunate individuals in the community who will derive no benefit whatsoever from successful development of technology enabling the modification of mtDNA in embryos. Furthermore, it is similarly incontestable that many more such individuals will have been born before there is any possibility of their benefitting from it. Surely the case for taking account of research into treating mitochondrial disease in this group and pursuing this line is abundantly clear?

Any scientific review of possible approaches to ameliorate the disaster inherent in some clinical manifestations of mitochondrial mutation will reveal, I submit, that the opportunities for treating, as distinct from preventing, mitochondrial disease are considerably greater. Acceptance of this proposition need not represent abandonment of research to curtail its transmission but recognition of the much slower progress likely to be a feature of that course.

Presumably the scientific members of any committees associated with this bill would be well aware of the current status of research on treatment of existing mitochondrial disease but I will briefly draw attention to a few features. There have been scores of reports over the last decade of trials of mitochondrial transplantation in experimental animal models. These have involved transplantation to a number of organs including heart, liver, lung and brain.

Mitochondrial functional capacities do not vary to reflect specific requirements of different organs and tissues. Their role is to generate energy and they can achieve this irrespective of the specific type of cell in which they are located. Consequently they can support the activity of any cell type in which they find themselves. On the

other hand however mitochondrial do express the self (histocompatibility) markers of the individual from whom they have been extracted and so are subject to recognition as 'foreign' and rejection by the immune system of any transplant recipient.

The goals of research which has been directed to developing treatment of existing mitochondrial disease have included controlling the recipient animal's immune response against mitochondria from genetically different donors, improvements in cryopreservation of donated mitochondria and developing reliable drug delivery systems. In a report of the clinical use of transplantation from Boston, paediatric patients with acquired (as distinct from congenital) myocardial muscle dysfunction experienced improvement after transplantation into the myocardium of mitochondria extracted from their own skeletal muscles. Given that the transplanted mitochondria were derived from the patient, immune rejection was not an issue in that trial.

As outlined above the specific tissue of the donor from which mitochondria are extracted should not limit the identity of tissue of the recipient into which they can be transplanted. Perhaps the location of disease in an individual carrying mutant mitochondria reflects the identity of the tissue carrying a higher proportion of mutants in that specific tissue? Occurrence of disease in one particular type of tissue of an individual who has inherited mutated mitochondria presumably reflects the luck of the draw – perhaps the type of tissue in which severe disease is likely to develop is a consequence of hosting a larger share of mutants.

I accept that politically connected individuals may have an approach which differs from that of those with a medical background to the identification of specific patients in the course of promoting an initiative (if one has any doubt about divergent attitudes between political and medical personnel, a moment's reflection on responses to the current pandemic could be enlightening). I suspect that some of the latter group would regard identification of a child who could not possibly benefit from the proposed initiative as crass. I believe that I would be in that group.

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