

25th ANNIVERSARY OF CLONING BY SOMATIC-CELL NUCLEAR TRANSFER

Cloning, mitochondrial replacement and genome editing: 25 years of ethical debate since *Dolly*

Andy Greenfield

Mammalian Genetics Unit, MRC Harwell Institute, Oxfordshire, UK

Correspondence should be addressed to A Greenfield; Email: A.Greenfield@har.mrc.ac.uk

This paper forms part of an anniversary issue on the 25th Anniversary of cloning by somatic-cell nuclear transfer. The Guest Editor for this section was Professor Kevin Sinclair, University of Nottingham, UK

Abstract

The birth of Dolly the sheep in 1996 elicited a tsunami of commentaries, both in the popular media and academic journals, including responses to the prospect of human reproductive cloning. Much of the anxiety expressed over this imagined consequence of Dolly's genesis revealed fundamental concerns about us losing our commitments to certain ethical goods, such as human dignity, or even 'what it means to be human'. Over the last 25 years, the focus of much of the ethical debate over human biotechnology has slowly shifted towards other genetic technologies that aim to influence inheritance, such as mitochondrial replacement techniques (MRT) and heritable genome editing. Genome editing, in particular, is a technology with multiple fields of application, actual and potential, in research and innovation. This review suggests that many of the fundamental concerns about the possibility of human reproductive cloning that were precipitated by Dolly persist today in the arguments of those who oppose MRT and any use of heritable human genome editing (HHGE). Whilst it is not accepted here that an understanding of human nature and dignity alone can demonstrate the ethical unacceptability of such assisted reproductive technologies, there are themes of justice, which extend into our relationships with animals, that demand continued wide-ranging examination and public dialogue. While Dolly has cast a long shadow over such discussions, this review suggests that the general existential angst over human uses of biotechnology that she came to symbolise is neither compulsory nor a reliable guide for how to think about biotechnologies today.

Reproduction (2021) **162** F69–F78

Introduction

A manuscript published in *Nature* in 1996 reported the cloning of sheep using somatic cell nuclear transfer (SCNT) into enucleated oocytes (Campbell *et al.* 1996). The donor nuclei were from an established cell line, which was itself derived from sheep embryos. The methodology included the induction of quiescence in the donor cells by serum starvation. This was an important result, in a fellow mammal, and the abstract of the paper speculated presciently on its significance for developing methodologies for modifying gene function in livestock species. It was also the latest step in understanding the molecular basis of cellular totipotency, pluripotency and the mechanisms of nuclear genome reprogramming that underlie these potentialities. Such fundamental developmental biology knowledge had been a driver of much research on cloning in a number of species over decades (McLaren 2000), a research trajectory that would eventually result in the ground-breaking report of direct reprogramming of differentiated cells into

pluripotent stem cells using a cocktail of transcription factors (Takahashi & Yamanaka 2006). But perhaps the most surprising aspect of the 1996 sheep cloning paper, from an historical and cultural perspective, is that this is not the paper about Dolly the sheep. Dolly was born in the July of 1996, but the paper reporting her genesis appeared in the same journal in 1997 (Wilmut *et al.* 1997). As the title makes clear, the 1997 paper reports the first use of adult cell nuclei, from the mammary gland, in successful SCNT cloning of a mammal. The biological significance is clear: the ontogenetic journey from embryonic to adult cell does not result in any irreversible loss of genetic information required for the development of a mammal to term. But what of the cultural significance of the report of the birth of Dolly the sheep? There was, as has been well documented in numerous commentaries, an extraordinary response. The world went mad about Dolly. Has a sheep ever had an obituary? (Whitfield 2003). Although some scientists felt that the advances reported in the 1996 *Nature* paper were more significant (Wadman 2007), it was *Dolly*,

the Finn Dorset cultural icon, who came to symbolise so much about the imagined hopes and hazards of biotechnology, including, but by no means exhausted by, possible uses of genetic technologies in agriculture; the promise of stem cell biology and regenerative medicine; the cloning of humans, interventions in the human germline and associated dystopian visions of our reproductive futures. It seems clear that scientists cannot control the historical and cultural context in which their data are produced, consumed and interpreted by a (sometimes) eager world.

This review explores some of the ethical responses to *Dolly*. In particular, it will examine continuities and discontinuities between the visions and concerns that clustered around cloning technology back in the mid-nineties, and some recent responses to two germline interventions in humans: heritable human genome editing (HHGE) and mitochondrial replacement techniques (MRT). These two have been chosen primarily because, rather than being just theoretical possibilities, they have actually been used to intervene in human reproduction (Zhang *et al.* 2017, Wang & Yang 2019), suggesting that future uses are not out of the question and may even be likely. The contemporary ethical landscape of debates over agricultural biotechnology and *Dolly*'s legacy here is also briefly considered. At the outset, however, it is made clear that there is one paramount ethical concern about SCNT reproductive cloning technology: its inefficiency. It is often noted that *Dolly* was the product of over 250 transfers of reconstructed embryos, the only lamb that survived to adulthood. Various strategies have been adopted in the intervening years to improve the efficiency of SCNT livestock cloning, but success rates are still low: somewhere between 1 and 5% of transferred embryos result in viable offspring (van der Berg *et al.* 2019). Abnormalities in offspring are also relatively common, varying between species, and these, like the low success rates, are usually attributed at least partly to imperfect nuclear reprogramming and consequent epigenetic abnormalities (Gouveia *et al.* 2020). The high attrition rate of late term pregnancies also constitutes a health risk to the surrogate dams. Overall, the health and welfare concerns associated with SCNT cloning, which affect the complete lifespan of the cloned animal, still persist to this day; whilst technological progress might improve efficiencies and reduce or even eliminate such concerns in future, they must be a significant element of any current ethical discussion of the use of SCNT in reproduction.

The meaning of *Dolly*: shared languages of opposition to human reproductive cloning and heritable human genome editing (HHGE)

The literature on SCNT has tended to distinguish between reproductive cloning, of which *Dolly* was an example,

and so-called therapeutic cloning, involving the use of SCNT embryos for the derivation of embryonic stem (ES) cells and other research purposes (Ethics Committee of the American Society for Reproductive Medicine 2016). Human ES cells from karyotypically normal SCNT embryos (NT-ES cells), which were first reported in 2013 (Tachibana *et al.* 2013a), may be used in addressing research questions concerning the establishment of totipotency and pluripotency but are also often cited as a potential source of autologous stem cells and tissue derivatives thereof, in patients requiring stem cell-based therapy, hence, the 'therapeutic' tag. Such research and innovation raises many ethical questions (Hyun 2011), especially concerning the potential for exploitation of egg donors and the status of the human embryo, and some commentators sensed a fairly early move from concerns about the possible use of reproductive cloning in humans towards distinct concerns about embryonic stem cell research and stem cell therapies (Wadman 2007). However, ethical questions about human embryos and stem cell derivatives have less of a grip on the public imagination in some parts of the world. By contrast, the idea that *Dolly* represents a cultural moment at which humanity saw the technical possibility of human reproductive cloning appears to be almost universal. This will be the focus in this section.

What were the objections, fears or concerns expressed by opposition to the prospect of human reproductive cloning? The author draws on the discussions in Hopkins (1998), Maio (2006) and Segers *et al.* (2019) as well as on personal experiences of discussing germline technologies in a variety of forums over the last 20 years. No attempt has been made to offer a systematic or comprehensive survey of the relevant ethical literature, which is vast. Nor is there a claim of any special authority concerning what really matters when discussing this topic: the themes that have been selected to discuss below are simply those that the author has encountered, as a scientist, on multiple occasions, in different contexts.

The media has historically reflected, or even been the source of, general existential angst over the possibility of human reproductive cloning, which around the time of *Dolly*'s genesis included the following themes, in no particular order and with some overlap in content:

- (i) *Human copying: the idea that cloning threatens human uniqueness, individuality and identity.* The clone, or replicant, has been explored repeatedly in science fiction literature and film. The term 'clone' evokes the loss of authenticity, loss of value, loss of dignity – it threatens our idea of humanity, of what it means to be human. Roughly, the term 'dignity', the use of which is complex (Segers & Mertes 2020), often tries to capture those morally relevant features of human beings that are immune to ethical trade-offs (GEAC 2019) and which merit respecting and honouring (The term is used here in an entirely secular sense, but religious uses are common). It is worth noting

that the fictional clone is often portrayed as easily brainwashed and evil, in contrast to the good original, as if she/he somehow manifests the troubled or corrupted moral provenance of the technology that led to their creation.

- (ii) *The Brave New World trope: the idea of cloning as the mass production of human identities.* Here, the emphasis is on the industrialisation and commodification of the human body, potentially for 'spare parts'. In Huxley's novel (Huxley 1932), 'Bokanovski's Process' is used to generate embryos that bud and proliferate, allowing production of 96 copies of a single progenitor. It is the *scale* of production, recognisably industrial, which is meant to alarm. And to what sort of use would the mass production of humans be put? In his 2005 dystopian novel *Never Let Me Go*, Kazuo Ishiguro explores the lives of young clones, produced to act as organ donors. Here, it is the contrast between the ordinariness of their lives, their essential recognisability and normality, with the extraordinary explanation for their existence and fate, that is designed to shock.
- (iii) *Parenthood and the design of children: reproduction with a particular purpose in mind.* A rational purpose of human cloning often cited as an example is to replace a child that is dying or has died – and the target of moral opprobrium here are the parents, apparently driven by some misguided sense of entitlement, who seek the 'replacement' child: 'Why can they not simply accept their loss? How appalling to be a mere replacement, and have that status inflicted by one's parents'. It is unclear whether such a child would regret its birth or resent its biological parent(s). There is also some irony here in the straightforward acceptance by many that a cloned child would be a 'replacement' for the original child, given the widespread opposition to genetic determinism i.e. opposition to the idea that we are our genes. It is received scientific wisdom that it may be possible to clone an individual's genes, but this would not amount to cloning that individual, characterised as they are by having a distinct personality or character (Ayala 2015).
- (iv) *The Prometheus trope: the portrayal of scientists and science as essentially problematic.* They seek fame, fortune and power, their hubris knows no bounds, and they impose their emerging technologies on an unsuspecting world by thinking how best to utilise their power rather than considering whether it is the right thing to do so, or so the story goes. Victor Frankenstein is perhaps the supreme literary emblem of scientific arrogance; it is unclear whether he represents the idea of the potential rogue inside all scientists. Everyday notions of truthfulness and the role of science and technology in the betterment of humankind are nowhere to be seen in such narratives.

Whether similar themes underlie concerns about the possibility of human reproductive cloning today is not clear. To some extent, this is because the ethical debate around the impact of biotechnology on 'the human' has moved from a focus on human reproductive cloning to the possibility of other germline interventions, such as altering genomic

DNA in a controlled fashion to influence the inheritance of human traits i.e. heritable human genome editing (HHGE). A recent international commission explored the science, including safety and efficacy, and, to some extent, the ethics of possible clinical uses of genome editing in human gametes and embryos as a means of avoiding the transmission of serious heritable diseases during assisted reproduction (National Academies of Sciences 2020). There have already been a number of publications that have carefully examined the ethics of HHGE, perhaps most notably from the US National Academies (National Academies of Sciences 2017), the Nuffield Council on Bioethics (NCOB 2018) and the German Ethics Advisory Council (GEAC 2019); this review will not survey those reports and their arguments, which to a degree focus on biological, social and political circumstances that could justify the responsible use of a safe and effective HHGE. Instead, it will briefly explore echoes of the above four themes in some of the contemporary rhetoric of ethical opposition to the very idea of HHGE.

The problem of 'scientific hubris' is prominent in discussions of HHGE. In his analysis of the scientific environment that, he argues, encouraged activities that led, infamously, to the birth of twins with edited genomes in China in 2018, historian Ben Hurlbut concludes that self-governing science is, in effect, rogue science, because it assumes the authority to identify what is good, when such a decision rightly belongs to society as a whole (Hurlbut 2020). Others (Dickenson & Darnovsky 2019) also believe that a particular 'culture' of science was complicit in the Chinese twin experiment, describing a permissiveness characteristic of the working environment of elite scientists; although, interestingly, this 'permissive science' characterisation is extended to the interdisciplinary working group of the Nuffield Council on Bioethics that reported on HHGE in 2018 (NCOB 2018), half of which comprised non-scientist members. So, claims about the culpability of an irresponsible scientific 'elite' and its supporters are very much centre-stage in contemporary ethical objections to HHGE. So too are concerns about the threat to human dignity posed by HHGE and the consequent requirement to create a public space for addressing questions of human integrity, rights, and dignity (Hurlbut et al. 2018). Contesting parental entitlements in this context is also common, especially claims stemming from the desire for genetically-related children, which is commonly dismissed as a valid justification for HHGE, because no such reproductive right exists (Baylis & Ikemoto 2017) and, besides, parents have alternatives if they wish to have healthy children, such as gamete donation or adoption (Andorno et al. 2020). Finally, whilst the threat of industrialisation is not a common theme in discussions of HHGE, the frequent use of the 'designer baby' trope in the popular media indicates that related concerns over commercialisation, commodification and lack of due appreciation for the 'gifted' character of children

persist, as do reasonable concerns over exploitation by unscrupulous clinics that might offer HHGE services of dubious safety, effectiveness and legality.

Potential explanations of the persistence of these concerns and attitudes across two decades and different biotechnological contexts will have to be deferred to another occasion. The author finishes this section by noting that whether one considers a future, safe and effective HHGE to be incompatible with human dignity and a just society depends on one's understanding of the term 'dignity' and one's conception of justice, which in both cases is already value-laden. For example, HHGE, if safe and strictly regulated, has been discussed as a possible means of preventing monogenic disease transmission in certain limited circumstances ([National Academies of Sciences 2020](#)). Anybody who has ever lost a loved one to cancer will understand the appalling insult to human dignity routinely delivered by that particular disease. The use of science in combatting such diseases is not only consistent with valuing human dignity, understood here as demanding a response to human physical and psychological suffering, but actually seems to be a requirement of a proper understanding of it. The question then remains whether disease prevention by assisted reproduction, which is not therapeutic, can be viewed as on a par with disease therapy in its significance for human flourishing. More about this in the next section.

Mitochondrial Replacement Techniques (MRT): cloning by another name?

MRT comprise a group of related embryological methods that can be used to prevent the transmission of pathogenic mitochondrial DNA (mtDNA) from mother to offspring, thereby avoiding serious, life-limiting mtDNA-dependent mitochondrial diseases ([Gorman et al. 2016](#), [Greenfield et al. 2017](#), [Herbert & Turnbull 2018](#)). In a discussion on legal prohibitions of human reproductive cloning, [Ayala \(2015\)](#) discusses the vote of the UK House of Commons that led to MRT being made lawful. Why is MRT considered by some to be relevant in the context of a discussion of human reproductive cloning? And has MRT unfairly attracted some of the moral ignominy commonly associated with human reproductive cloning? These are questions that will be addressed in this section.

The two most common versions of MRT consist of maternal spindle transfer (MST) and pronuclear transfer (PNT), which are performed pre- or post-fertilisation, respectively. In MST ([Tachibana et al. 2013b](#), [Kang et al. 2016](#), [Yamada et al. 2016](#)), the spindle containing the maternal chromosomes is transferred from the prospective mother's metaphase II-arrested oocyte into a donor oocyte from which the spindle has been removed; in PNT ([Hyslop et al. 2016](#)), the newly formed pronuclei are transferred to a fertilised donor egg from

which the pronuclei have been removed. In both cases, the donor egg is from a woman free of pathogenic mtDNA, resulting in a reconstructed embryo that has substantially normal mtDNA and minimal levels of the prospective mother's pathogenic mtDNA, which has been 'replaced'. The decision to make MRT lawful in the UK, and its subsequent regulation by the Human Fertilisation and Embryology Authority (HFEA), were dependent on a number of assessments of pre-clinical safety and efficacy data, including animal model and human research embryo data as well as public engagement over its ethical acceptability ([HFEA 2016](#)).

The fact that transfer of nuclear DNA is central to both MST and PNT might suggest a close similarity to somatic cell nuclear transfer. But does this similarity extend to the aims of using MRT and SCNT and their imagined places in human reproduction? The fact that [Ayala \(2015\)](#) discusses these technologies together suggests that some see them as 'from the same stable', in some sense. Of course, they do share some safety and efficacy considerations, given that both involve transfer of nuclear DNA from one cell to another, with a view to generating a zygote that is competent to develop further. Things could go wrong and concerns over the safety of MRT have been expressed. These include, for example, premature oocyte activation and aneuploidy, carryover of pathogenic mtDNA into offspring and also possible negative impacts on the finely tuned functional interaction between the nuclear genome and mtDNA ([Morrow et al. 2015](#)). The inefficiency of mammalian SCNT, discussed earlier, may suggest to some that MRT is likely to be similarly inefficient and risky; but MRT involves the transfer of meiotic or zygotic genomes into familiar cellular contexts and the particular risks associated with extensive reprogramming of the differentiated adult cell nuclear genome do not arise. Moreover, pre-clinical and (very limited) clinical data suggest an efficiency that is acceptable for controlled clinical use of MRT to prevent mitochondrial disease transmission in certain limited circumstances, with strict regulatory oversight ([HFEA 2016](#)).

How might we think about MRT in terms of its significance to those who want it and campaigned for it to be made lawful? The author wants to suggest that it is an assisted reproductive technology that permits a new move in an old and familiar reproductive space, scientifically and socially. MRT is sexual reproduction, albeit unusual in its mechanism, generating a unique individual; it is not a form of parthenogenesis. It is one way in which women at very high risk of transmitting serious mitochondrial diseases hope to 'have children' free of disease. 'Having children', which are here biological children, is meant to remind us that the ambition of these women is recognisably ordinary. They want to have children that will be like any other healthy child. A woman having MRT will be related to the resulting child, sharing family resemblances – but only resemblances – with it, in the standard fashion. Creating

and enjoying such relationships is a custom of profound significance to many, reflecting the importance of sexual reproduction (and all it entails) in our biological and cultural history. So, seeing close similarities between MRT and SCNT here is to focus only on the mechanics of the procedures. If one focuses instead on the intended purpose of the methodologies, one sees significant differences: MRT is used (under UK legislation) with the intention of preventing transmission of a serious, life-limiting disease from mother to child, who would be related in the conventional manner; SCNT, if used to establish a pregnancy (illegal in the UK and most jurisdictions) for any purpose, would create a child that is a 'clone' of the somatic cell donor. But, leaving to one side the obvious fact that SCNT would not be a good option for preventing mtDNA transmission, as it is still a highly inefficient process and unlikely to result in a live birth, how would we characterise this possible intervention and its place in human lives? Sexual reproduction, including use of MRT, is one way (there are others) in which humans commonly express their desire to have children and create families; by contrast, the desire for asexual reproduction – for cloned children that are near-identical genetically to one parent – finds no expression in ordinary human lives. Rather, it is currently a theoretical desire, one whose qualities are more likely to be discussed by a philosopher, given that it is not anchored in everyday practices and customs that indicate its significance and value to humans.

These distinctions do not, of course, constitute a 'knock-down' argument against the moral acceptability of reproductive cloning in all circumstances. A future technology might permit safe human reproductive cloning, and a corresponding desire for its use might emerge in its wake, and perhaps even become common. Proponents might argue that it is justified in some circumstances. But making the case for or against cloning in such circumstances is unlikely to hinge on anything one might say about MRT specifically, unless again one confuses surface procedural similarities with the character of the underlying desire. Noting that MRT involves nuclear genome transfer and is lawful in the UK would not make a significant contribution to an ethical argument for pursuing human asexual reproduction; that would require other argumentative moves to be made, reflecting other human needs, desires, beliefs and values. So, we see that comparisons between SCNT and MRT should be made only with utmost care to distinguish mechanical from ethical and social aspects, where our ethical understanding is seen to be sensitive to ordinary ways in which humans realise their capabilities, how these can reveal what matters to them and can constitute social norms, but without conflating conventionality with demonstrable moral justification.

Nonetheless, some commentators have refused to use the term 'MRT' and instead insist on 'human nuclear genome transfer' to name the technique (Baylis 2017).

It is argued that 'MRT' is a camouflage term, designed to obscure the fact that MRT relies on micromanipulation techniques that are required for SCNT too (Baylis 2017). It is suggested here that this similarity in the techniques of MRT and SCNT should not be central to our ethical considerations: it is the intention with which MRT (or a possible future SCNT) is performed that is most significant in this context, not features of the methodologies employed. But the question then arises: why prefer the term 'MRT' to 'human nuclear genome transfer', if this is the case? The answer presumably relates to the issue of framing, so common in contemporary bioethics. If one wants to draw attention to the fact that MRT is being used with the intention of preventing transmission of mitochondrial diseases to offspring, the term 'MRT' does that rather neatly. If one wants to draw attention to the fact that MRT comprises micromanipulation techniques which, if perfected, may lead, almost imperceptibly, to the legitimisation of other interventions in the human germline, including reproductive cloning (or HHGE), then 'human nuclear genome transfer' is perhaps preferable.

It has been noted elsewhere that an ethical evaluation of MRT requires more than an examination of the role of language and framing when it is debated (Greenfield 2020); and one way of doing so is by offering a refutation of the existence of a parental entitlement to genetically-related offspring, satisfying some sort of 'unmet need' that would underpin the justification of developing MRT, with associated research, law-making and regulations, especially when defending this entitlement requires the use of limited healthcare funds (Baylis 2017). Such objections, thus, fundamentally relate to issues of social justice and solidarity, which some see as threatened by human germline interventions. Distributive justice is an important issue here – equity of access to new technologies, for example, is likely to be a significant factor in their acceptability – and requires close examination. But the author does not see objections that focus on the significance of the desire for genetic relatedness, or 'mere' desire, as helpful. First, for most of human history no such desire existed, strictly speaking, given that we knew nothing about genetics. So, care is required in how we characterise this desire. Secondly, there may be no existing legal right to a genetically-related child, but this situation might change. For example, the protection of a woman's right to have access to safe and effective contraception has a legal history – no such right would have been widely recognised 60 years ago (and still isn't in some parts of the world). Today, it is possible to see access to free or affordable contraception, the choice of whether or when to 'have children', as an expression of a woman's dignity. The World Health Organisation (WHO), quite rightly, states that there is still an unmet need for contraception, especially among the most vulnerable in society, because 'in the least developed countries, 6 out of 10 women who do not want to get pregnant, or

who want to delay the next pregnancy, are not using any method of contraception' (WHO 2014). But note that the word 'want' is used twice in this justification of the existence of an unmet need. This is entirely acceptable, because there is no clear (and value-free) way of distinguishing between fundamental human desires and human needs. Our desires, especially in the context of reproduction, deeply reflect our capabilities and what matters to us in life – the roles that their satisfaction play in human flourishing are not something to be marginalised or problematised during academic ethical debate. It is possible that we might in the future come to recognise the 'right' to a genetically-related child, rather than see it as some sort of unfortunate cultural artefact (Greenfield 2018). Perhaps we will recognise it as a way of protecting the choice of how to have children. We may even come to see such a right as flowing from a deeper understanding of human dignity. And in general, the author does not think the law, including international law, should be used as an infallible guide to what is ethically acceptable.

Finally, it is worth briefly considering certain thought experiments, relating to the public acceptability of MRT: what if MRT required (due to the alternate biology of some other possible world, where, for example, maternal spindles and pronuclei are simply too fragile to move) the transfer of the nuclear genome, not around the time of fertilisation of the prospective mother's egg, but later in its development, such as at the 8-cell embryo stage? If we also imagine that embryonic nuclear genome reprogramming would be safe and efficient in these circumstances, it would then be possible to make up to eight attempts at embryonic nuclear transfer into donor oocytes; but it would also mean that up to eight genetically near-identical twins could be produced. Would this form of 'micro-cloning' – constrained in the numbers of genetically identical children that could be produced, but now recognisably more similar to the SCNT procedure – have been acceptable? What if the 2-cell or 4-cell embryo were the only sources of stable nuclei? We will probably never know the answer to such questions, based as they are on counterfactuals, but it seems that, although this would still amount to sexual reproduction by the mother and her partner, familiar anxieties over the possibility of reproductive cloning, considered earlier, may have contributed to the public acceptability of MRT in such circumstances.

Dolly in the age of genome editing: using genetic technologies in farmed animals

It is often in combination that the power of new technologies is realised. This seems especially relevant when considering farmed animals like Dolly. When combined with genome editing in somatic cells, SCNT promises to facilitate the generation of animals with highly sophisticated, edited genomes. As an example,

CRISPR-Cas9 editing of all 62 copies of porcine endogenous retroviruses (PERVs) has been reported in a porcine kidney epithelial cell line, resulting in their inactivation (Yang *et al.* 2015); subsequently, a porcine primary cell line in which all of the PERVs had been inactivated by genome editing was used to generate PERV-inactivated pigs via SCNT (Niu *et al.* 2017). Such pigs form part of the wider project of utilising pig organs for xenotransplantation in humans, by overcoming concerns about cross-species transmission of PERVs. Concerns about immunological compatibility remain to be resolved (Yang & Wu 2018).

Beyond the use of large animals for biomedical purposes, there are a number of compelling proposals to alter their genomes for introduction into the food chain – to allow production of fitter, healthier and more productive farmed animals (Tait-Burkard *et al.* 2018). Such uses of genome editing are often recommended as a response to the global challenge of food security, or even climate change, with opportunity costs to consider if they are rejected. As with the topic of the reproductive use of SCNT in humans, however, the possibility of altering the germline of farmed animals – of sculpting the inheritance of traits of interest to farming – inevitably raises ethical questions. These are likely to be highly complex and contentious, since we are discussing a combination of three components that already raise ethical questions in isolation: human treatment of animals, the nature of farming and food production, and germline technologies such as SCNT and genome editing. In this final section, the author will briefly consider two ethical concerns that were discussed during a project on genome editing and farmed animals being undertaken by the UK Nuffield Council on Bioethics, since they raise interesting complexities. The Council will ultimately make policy recommendations in this area, based on its deliberations.

Might genome editing entrench intensive farming practices?

A number of proposed uses of genome editing, unrelated to influencing productivity traits, have animal welfare benefits as an outcome. For example, the naturally occurring POLLED variant, which results in hornless cattle, has been recapitulated by genome editing in cell lines and, following SCNT, these have led to the birth of hornless dairy cattle (Carlson *et al.* 2016). If introduced by genome editing into elite breeds, the POLLED allele will eliminate the need for painful dehorning and disbudding and protect animals and their handlers from horn damage (Mueller *et al.* 2019, Van Eenennaam 2019). Edited alleles conferring disease resistance, such as the *CD163* gene edit that confers resistance to porcine reproductive and respiratory syndrome (PRRS) (Burkard *et al.* 2018, Yang *et al.* 2018), also promise to reduce animal morbidity and mortality.

One additional consequence of widespread uses of such genome-edited animals in the farming system would be the ability to maintain animals at high-stocking densities, a characteristic of intensive farming methods. Opposition to intensive farming appears to be growing in some countries, due to its perceived negative impacts on animals, soil, some farmers, the wider environment and climate change. So, the possibility emerges that our ethical response to such uses of genome editing depends on the register in which we consider its impacts; we might acknowledge the positive impacts on individual animal welfare, yet, regret the further entrenchment of intensive farming methods (and their consequences) that it apparently facilitates. Resolving such tension requires that more attention be paid to the nature and urgency of the global challenge of food security and how best to respond to it, considering technological responses alongside other interventions. It will be difficult, nevertheless, given this systemic complexity and the potentially unpredictable reverberations of interventions in the system, to isolate the question of whether editing the genome of a farmed animal with the aim of improving welfare is ethically justifiable in certain circumstances.

Might sophisticated genome editing undermine animal dignity?

As we have seen, genome editing and SCNT have already been used in combination to generate animals with multiple edits. Such oligogenic/polygenic editing, which in future may not require use of SCNT, might be used to introduce several disease-resistance variants and other favourable traits. But if we let our scientific imaginations wander, what sorts of animals might we be able to create in future, following such large-scale editing? Could we change the behavioural dispositions of animals through editing of genes functioning in the central nervous system (CNS)? Would it be possible to produce an animal, a chicken, for example, that does not want to explore or roam and prefers to be in a confined space with other animals? Might we be able to alter animal responses to painful stimuli, such that they no longer suffer during routine husbandry, including dehorning, castration or branding? Going further, can we conceive of animals entirely lacking a CNS capable of supporting sentience, such that they effectively constitute biological reactors for the production of meat or milk but with no possibility of suffering? Would we recognise such entities, with such altered or diminished capabilities, as animals?

Alongside such exercises of our scientific imagination, we might be minded to exercise our moral imaginations too. Would such applications of genome editing constitute a failure to recognise the inherent dignity of animals? As we have seen, we tend to associate the use of the word 'dignity' with humans, but some authors have discussed the animal equivalent. We can conceive of a

dog being mocked or turned into an object of ridicule by having graffiti spray-painted on its fur (Anderson 2004), and object to someone spitting on animals or laughing at them when they hurt themselves (Abbate 2020). Such 'dignitary harms' need not negatively impact the experience of the animal, how it feels, nor affect its welfare in a conventional sense. Would the generation of anencephalic chickens for meat production constitute a dignitary harm, one that might lead to further such harms? Or is it a reasonable response to the human need for dietary protein? The answer to this sort of question is likely to depend on one's attitude to animals, in different contexts, and what can legitimately be done to them by humans, in the interests of humans. These are deep waters. The harms that we inflict on animals, in diverse circumstances, are likely to exist on a spectrum of acceptability. This spectrum extends beyond the relatively straightforward (in hindsight) example of Dolly: the product of biomedical research that contributed to the larger project of stem cell biology and regenerative medicine, with a view to alleviating human suffering. But somewhere on this spectrum, in some context, we may cross a threshold beyond which we will be accused, perhaps by future generations, of failing to recognise that animals too have a dignity that makes demands on our behaviour. Of course, we have moulded the genomes of the animals we farm over thousands of years of selective breeding, in ways that needed no sophisticated technology. We start with these domesticated animals at the centre of our considerations, already some way down the track of animal genome manipulation in our interest. But we must continue to ask the question: how far should we proceed down this path?

Summary and conclusions

This review began with a section that indicated the persistence of fears concerning the potential negative impacts of using genetic technologies in humans, often characterised by a reliance on notions of human nature, dignity and what it 'means to be human'. Some of these themes emerging from responses to *Dolly* and the possible human biotechnological interventions that she came to symbolise, and the ways in which they were and are expressed, suggest the existence of an unusual ethical backwash, from imagined dystopian futures, that taints and distorts considerations about whether and how to employ technologies such as MRT and HHGE today. The author suggests that the generalised existential angst that characterises some of those responses in the popular media is not compulsory. Whatever the technical similarities between MRT and SCNT might be, there are features of MRT that the author thinks make it a recognisable extension of widespread human reproductive behaviours and norms: allowing sexual reproduction and the birth of a genetically-related (not near-identical), disease-free child. These

distinguish it from reproductive cloning in a way that is significant for how we discuss its place in human lives. MRT may appear odd, as the alternative label '3-parent IVF' invites us to conclude, but so once did IVF itself. Similar comments could be made about theoretical uses of HHGE to prevent transmission of serious monogenic diseases in certain circumstances. The question remains whether we could ever come to see a safe human reproductive cloning technology as in some way capable of supporting human flourishing in future, in ways that perhaps express fundamental human desires or needs in a just fashion. The author rejects the idea that a positive case can be made for asexual reproduction by SCNT in the same way that it can for sexual reproduction by MRT, even if the SCNT cloning was proposed as a means of preventing mitochondrial disease transmission.

The author suggests that notions of the 'meaning' of being human, or human dignity, do not allow us to capture the issues here in a way that is decisive: it is possible to have conceptions of human dignity and 'the meaning of human life' that are entirely consistent with our using technology that intervenes in our biology, including in our DNA, in certain circumstances and contexts, but not all. The enemy here, of course, is the tendency to generalise about the possible impacts and significance of such interventions. Moreover, what we take to be compatible with human dignity or meaning is already informed by our ethical commitments. Our understanding of what is required by justice, particularly when conceived as fairness, will be central to defining those circumstances in which MRT and HHGE can be considered acceptable. And, whilst a focus on human dignity might obscure this, considerations of justice extend to our treatment of animals. *Dolly*, perhaps, forces us to remember this. There are difficult questions to answer about how farming should evolve to meet diverse human needs in ways that are compatible with high standards of animal welfare and respect for human and animal dignity. But these are questions that we are still struggling to articulate, let alone answer.

The author has noted some of the ethical objections to cloning and germline alterations in a number of fields, objections that go beyond standard considerations of safety, efficacy and the immediate welfare concerns of individuals produced by such technologies. There will need to be continued discussion of these issues and many others by academics, other stakeholders and the wider public, preferably with a degree of granularity that respects important differences between possible applications. But since we are discussing technologies that may change the way we think about ourselves, about animals and about food, public dialogue will play a major role in determining whether these interventions are politically acceptable and in which circumstances (Dryzek *et al.* 2020). Those circumstances will need to identify clear anticipated benefits, an acceptably low risk of harm, and a general sense of societal

interest. Governance and regulatory mechanisms will be required to ensure such outcomes. It seems clear, however, from the debate about public health strategies in response to the Covid-19 pandemic that what is in the public interest, indicated by a combination of scientific data and political judgments about their significance for policy, is not necessarily what the public want or would choose. Those, like the author, who think that innovation using genetic technologies can help us rise to some global challenges – biomedical or agricultural – and support human flourishing more generally, will need to continue to make the case, avoid hype and excessive generalisation, respectfully engage with the counter-arguments of opponents and do so using language that is clear and accessible. Hopefully, *Dolly* will serve as a reminder of the importance of such wide-ranging dialogue.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Acknowledgements

The author thanks the Medical Research Council for supporting his research programme in sexual development through core funding to the Mammalian Genetics Unit at MRC Harwell (MC_U142684167) and thanks colleagues at Harwell, the Nuffield Council on Bioethics and its working groups, the HFEA, the National Academies International Commission on Heritable Human Genome Editing and other colleagues for wide-ranging discussions about the issues covered in this commentary. The author gives special thanks to Lydia Teboul, Sara Wells and an anonymous referee for comments on the manuscript. Opinions expressed are the author's and not necessarily those of any organisations with which the author is associated.

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Received 30 November 2020

First decision 1 February 2021

Revised manuscript received 1 March 2021

Accepted 20 April 2021