Embryonic stem cells without moral pain?

Health Council of the Netherlands

Centre for Ethics and Health

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Centre for Ethics and Health

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This report

This report has been drawn up by the Health Council's Standing Committee on Medical Ethics and Health Law (see Appendix 1 for composition).

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Summary

This spring, Korean researchers announced that they had succeeded in obtaining stem cells from embryos produced by cloning. This involved introducing the nucleus of human skin cells into egg cells from which the nucleus had been removed. It is hoped that in the long term this method can be used to culture patient-specific cell material for autologous transplantation that might prove effective in the treatment of a wide range of complaints. At present, the research is still in its initial stages. However, this research and its possible applications are controversial. Firstly because human embryos are produced that will only be used as a source of stem cells. And secondly because (a large number of) human egg cells are required for the cloning procedure. The question is whether these can be obtained by morally acceptable means. While the discussion is still under way, research of this kind is forbidden in many countries, including the Netherlands.

Against this background, interest has recently arisen in the possibility of obtaining the same result (patient-specific pluripotent stem cells) without the necessity of producing human embryos or asking women to donate (mature) egg cells for this purpose. The ethically most attractive approach is the 'direct reprogramming' of body cells without the intermediate step of embryo production and without the need to use egg cells. This approach, however, seems to be the one that lies furthest in the future. Moreover, it may prove to be necessary to produce human embryos in the development of this approach too.

Many of the other 'embryo-saving' proposals presented in the literature are based on the assumption that non-viable embryos are not strictly speaking embryos at all, so that the harvesting of their contents does not raise any moral issues. It may be asked whether this is not an unduly facile approach to the problem. What is in fact the status of the non-viable embryo? It seems undesirable to incorporate an answer to this into the formal definition of an embryo. This is however precisely what is done in the current Dutch Embryos Act.

One of proposed ways of getting round the egg-cell problem is to culture the egg cells required from embryonic stem cells. This approach, however, still raises ethical issues when one considers that genetic material cultured from stem cells could also be used for reproductive purposes. This (still speculative) scenario might make it possible to provide better support for couples with fertility problems, but would in its turn represent a major challenge to our traditional ideas about the natural limits of reproduction and parenthood.

However, the primary policy context for this report is the impending evaluation of the Dutch Embryos Act and the discussion of the desirability of rescinding the (temporary) ban on the creation of embryos for other purposes than pregnancy. Far from making this discussion unnecessary, the quest for 'embryo-saving' sources of tissue-matched stem cells only underlines the fact that this discussion can no longer be postponed. The evaluation of the Act must also include consideration of what precisely is to be understood by the term 'embryo'.

Embryonic stem cells without moral pain?

1 Introduction

Newly formed heart muscle cells that can help repair a damaged heart and newly formed dopamine cells that can limit the effects of Parkinson's disease. These are two examples of possible future applications of regenerative cell therapy. It is hoped that therapies of this kind can be developed by investigating the possibility of using stem cells to create various types of tissues.

Embryonic stem cells

There has been considerable discussion of which types of stem cells are most suitable for this kind of research. 'Pluripotent' stem cells from human embryos seem to have the greatest potential for development (Odorico 2005). However, promising results have also been obtained in the meantime from 'multipotent' stem cells from tissues taken from adults (bone marrow, for example), aborted foetuses and umbilical cord blood (Henon 2003, Rogers 2004). Despite the favourable results obtained using 'somatic' or 'adult' stem cells of this kind, the broad scientific consensus is that research using human embryonic stem cells is essential. This was also the tenor of the Health Council's recommendation (Health Council 2002).

The use of embryonic stem cells is, however, controversial. The ultimate source of these cells are human embryos, which are destroyed when the cells are harvested. In view of the possible significance of the research to future patients, many people consider that this is not necessarily unacceptable, at least in the case of 'surplus' embryos produced during IVF treatment that would not survive in the long term. The moral discussion is focused mainly on the question of whether it can be acceptable to create human embryos specifically in order to obtain stem cells. This is necessary in order to cultivate stem cells with the identical tissue type as the patient undergoing treatment, so as to avoid rejection symptoms when the cells are transplanted.

The technique used here, *Somatic Cell Nuclear Transfer* (SCNT), also goes by the somewhat confusing name of 'therapeutic cloning'. The technique involves transferring the nucleus of a cell taken from the patient's body (the person requiring treatment with the cell material) into a donor egg cell from which the nucleus has been removed. The result of the cell nucleus transplant is the production of an embryo. This embryo is then used as a source of stem cells for autologous cell

therapy. 'Autologous' means that the transplant material, created via the intermediate stage of an embryo, has been cultivated from cells taken from the patient himself/herself.

Research into this area is still at an early stage. Korean scientists have meanwhile succeeded in obtaining patient-specific embryonic stem cells via SCNT (Hwang 2005). Further investigation, looking into (among other issues) the safety of using such cells as a source of transplant material, is needed before any thought can be given to clinical applications.

The normative debate

The creation of embryos for research or therapy raises moral issues for two reasons (Health Council 1998, German National Ethics Council 2004). The first reason has to do with the debate on the moral status of human embryos. Almost everyone believes that human embryos have a moral significance distinguishing them from all other human cells, and that they deserve a certain level of protection. This implies, at the least, that scientific or therapeutic use of embryos must be justified. A second moral issue relates to the need for donor egg cells for these applications and the question of how they can be obtained in a morally acceptable manner. If SCNT does turn out to be a practical way of carrying out autologous stem cell therapy, then the shortage of egg cells would become more keenly felt. The fear has been expressed that women would then be placed in a position where they would have to 'defend their right to physical integrity against the scientific and medical demand for egg cells' (Ethics Council 2004).

The Dutch Embryos Act (2002) prohibits the creation of human embryos for purposes other than pregnancy (Section 24a), but this ban is temporary[1]. As stipulated in Section 33, it will expire on a date to be set within five years after the Act entered into force (thus, before 1 September 2007). As the present coalition has agreed to take no action, the question arises as to whether that time frame can still be honoured. In any event, the debate as to whether the ban needs to be, and if it is desirable for it to be, lifted will be a matter for the next government.

In its opinion 'Stem cells for tissue repair', the Health Council pointed out some years ago that research into embryonic stem cells had not yet advanced to such a point that the prohibition in Section 24a impeded the actual development of therapies, but that this might eventually be the case (Health Council 2002). Furthermore, researchers stress that SCNT is important not only for the development of cell therapy, but also in many forms of fundamental research into developmental biology (Novak 2004, Hwang 2005). Similar points were also made in the reasons given for the recent decision of the Research Licence Committee of the UK Human Fertility and Embryology Authority for permitting research in which embryos are created via cell nucleus transplant (HFEA 2004). The United Kingdom is so far the only Western European country to give the green light to this research. As is the case in the Netherlands, but with the exception of Belgium, other European countries have imposed a statutory prohibition. Most research in this field is conducted outside

1 For a translation of relevant sections of the Act, see Appendix 2.

Europe, in regions such as Asia (Korea). The United States has outlawed the use of federal funds for research involving the creation of human embryos.

Though the debate on the acceptability of SCNT has certainly not yet been resolved in countries where research of this kind is prohibited (Europe) or permitted only to a limited degree (US), scientists do increasingly feel impeded by these restrictions. This is shown by the recent interest in attempts to release research on embryonic stem cells from the grip of this moral and legal discussion (Mandavilli 2005, Murray 2005). A fascinating search has started for morally unobjectionable sources of embryonic stem cells that can be used in autologous cell therapy. It is a dual search as it attempts to get around the problems posed by embryos as well as by egg cells.

This report

This report contains a discussion of the quest for morally painless variants for, or alternatives to, SCNT. It considers various techniques and approaches, all of which are currently speculative to varying degrees and that require further detailed investigation. None of them are feasible at this time. Many of the proposed solutions themselves raise other moral issues: human-animal combinations, the cultivation of embryos that cannot develop further than is needed to harvest stem cells, and the cultivation of egg cells from stem cells. The review presented in this report fits well into the task that the Health Council has set itself of drawing attention to issues in this area.

But that is not the most important reason behind this report. The developments referred to above raise the question of whether we have a clear moral and legal definition of what we understand by a (human) embryo. The response to this question given in the Embryos Act does not appear to be properly tailored to scientific developments in this field. The legal definition excludes too much, but it also perhaps includes too much. This is an important observation in the light of the future debate as to whether the ban in Section 24a should be lifted, as well as this year's scheduled assessment of the law.

The report's structure is as follows: we first address the two key moral questions associated with stem cell research for which embryos have to be specifically created. Section 1.2 looks at the moral debate on the status of the embryo. Section 1.3 investigates the scarcity of egg cells as a moral and practical problem. The later Sections summarise recent attempts to release research into embryonic stem cells from the grip of these two problems. Section 1.4 lists the proposed variants of SCNT and alternatives to this technique that (it is claimed) do not involve the creation of human embryos. Section 1.5 looks into 'female-friendly' methods: variants or alternatives in which women do not have to be asked to donate (ripe) egg cells. But the discussion of this two-pronged attempt to escape moral pain brings fresh moral issues to light. These are discussed in Section 1.6. The implications of all these issues for the Embryos Act are addressed in Section 1.7. The report ends with a number of agenda points set out in Section 1.8.

2 The moral and legal status of pre-implantation embryos

Is it acceptable to create human embryos as a source of stem cells for cell therapy? The answer that anyone gives to this question also shows the position they take in the debate as to the moral and legal status of human pre-implantation embryos (Holm 2005). The pre-implantation phase comprises the earliest stage in embryonic development, from fertilisation to implantation in the womb. An embryo that is placed in the womb in time is fully implanted after about fourteen days of development. As it is not possible to keep human embryos in culture outside the womb for more than a few days, the debate centres on what can and cannot be done with human embryos kept in vitro during the first few days of their development.

Moral status

The general consensus in the Netherlands is that human pre-implantation embryos have a definite value by virtue of which they deserve protection (Health Council 1998). This protection includes the principle that embryos must not be used or created for trivial purposes. However, it does not extend as far as precluding their use for important scientific or therapeutic ends.

The limited degree of protection conferred on pre-implantation embryos is often expressed in terms of an intrinsic value that embryos have as a result of their ability to develop into a human being. This value is set at a relatively low level as a reflection of the very early stage of development at this time (De Wert 1987, Hermeren 1996, Sporken 1979, Warnock 1984). Another view holds that the (limited) protection offered to human pre-implantation embryos is based not on an intrinsic, but on a symbolic, value. In this case, embryos do not deserve consideration for their own sake but rather as an expression of the views of the society that regards them as the initial form of human life (Den Hartogh 1993, Sandel 2004).

Against this view that embryos are 'deserving of limited protection', there is the opinions of some people that human embryos must be treated as persons from the point at which they are created. Of course, this attitude ('deserving of complete protection') leaves no room for the use or creation of embryos for purposes other than the goal of allowing them to develop into human beings.

An important variant of this view is the Roman Catholic doctrine, according to which the personhood of a human being lies not in any perceptible ability, but rather in the unity of body and soul that is assumed to exist from conception (Donum Vitae 1987).

An associated view derives from Aristotelian philosophy, in which the decisive point is that even though human embryos are not themselves yet (complete) persons, this is what they are designed to become. They are 'potential persons'. This potentiality is more than just a possibility or probability dependent on external factors. This view is based on the idea that what makes human embryos potential persons is not simply a matter of what they can

develop into, but rather that they are naturally directed to evolve into full human persons (Reichlin 1997). So potentiality is not here seen as a mere possibility ('passive potentiality'), but rather as the fulfilment of an intrinsic end ('active potentiality'):

> (...) the zygote is not a potential human being in the sense of 'could become', but a living and individualised organism with its own internal program, that has the intrinsic potential to develop in the species-specific way. In realising this intrinsic potentiality, the zygote depends on the external environment, but it assimilates the external stimuli according to its own laws of development (Jochemsen 2004).

The assumed dynamic continuity between what the embryo will become (if no external factors impede its development) and what, in it's active directedness towards this end, it actually is at the moment is the foundation for the view that human embryos have the moral status of human persons and must be treated accordingly (Eijk 1997). Some people take the view that embryos deserve complete protection only from the point (after about fourteen days) when they can no longer split up and can therefore be said to have a fixed individuality (Ford 2002). However, others consider that this is not a relevant criterion and emphasise that human embryos deserve complete protection from the point of conception (Jochemsen 2004, Vélez 2005).

None of the views on the moral status of embryos draw a distinction that is based on the manner in which they were created. Embryos produced by embryo splitting or (variants of) SCNT are as equally deserving of protection as are embryos created by fertilisation. The value of the embryo rests on what it can become or what it (potentially) already is.

Legal status

What is the legal status of the human (pre-implantation) embryo? Under Dutch law, an embryo (or foetus) is not a human person and there is no legal principle whereby it should be treated as such. Human beings only become part of the community of law at birth (Leenen 2000). A recent important decision by the European Court established that the 'right to life' protected under Section 2 of the European Convention on Human Rights (ECHR) did not extend to the unborn child (European Court of Human Rights 2004, Hendriks 2004).

This does not, however, mean that unborn life has absolutely no legal protection. According to the theory of 'progressive legal protection', current in Dutch health law, the extent of such protection depends on the stage of development that the embryo or foetus has reached. The first milestone that applies is implantation, which is completed after about 14 days.

Prior to this, an embryo is in 'status potentialis' (Leenen 2000, Te Braake 1995). In this earliest phase, an embryo has a limited degree of legal protection by virtue of it's 'generation from human gametes and potential to develop (...) into a human being'. Leenen and Gevers emphasise that 'potential' is to be understood with this in the passive sense, as described above. This involves

'(...) no more than that fused gametes have a potential; they may produce a human being if a number of conditions are met, but this need not necessarily happen' (Leenen 2000).

This theory of progressive legal protection is the foundation of the Embryos Act, which lays down rules for the treatment of human gametes and embryos. The law allows the use of surplus pre-implantation embryos created for IVF in research and therapy, subject to conditions relating to (among other things) proportionality and subsidiarity. But, creating embryos for purposes other than pregnancy is (provisionally) prohibited under Section 24a.

The definition of an embryo in Section 1c – 'cell or collection of cells with the capacity to develop into a human being' – was chosen to cover embryos created by methods not involving fertilisation (for example, through SCNT). The 1993 Bill still defined an embryo as 'the result of the fusion of human gametes prior to birth'. Similar definitions appear in German and British legislation dating from the same period. The birth of the cloned sheep Dolly in 1997, showing that SCNT could probably also create human embryos, raised the issue in those countries of whether the law also applied to these embryos (German National Ethics Council 2004, Morgan 2004).

The explanatory notes to the Dutch Embryos Act make the following comments on the definition:

> Scientific progress has allowed embryos to be created in various ways. However, the degree of protection that an embryo enjoys depends not on how it is created, but rather on its capacity to develop into a human being.

The definition used leaves room not only for all possible techniques for creating an embryo, but also for various views as to the significance of the fact that human embryos have the capacity to develop into a human being. Referring back to the distinction raised earlier, this 'capacity' can be regarded as both passive, as well as active, potentiality. However the latter view, insofar as it implies that human embryos are deserving of full protection from conception, does not accord well with the content of the Embryos Act.

3 Dependence on donor egg cells as a moral and practical problem

An important problem facing all forms of research and therapy that involve the creation of human embryos (not only SCNT, but also research in which embryos are created by IVF) is the issue of how enough egg cells can be obtained in a morally acceptable way. The Health Council's IVF Committee was split on the issue of whether it could be acceptable to ask women whether they wanted to take part in scientific research by acting as egg cell donors, which would require them to undergo the burdensome and not entirely risk-free process of hormone stimulation (Health Council 1998).

The Committee noted that this issue was not of great practical significance, as few women were expected to consider such a request. It then discussed a few alternative ways of obtaining ripe human egg cells for research. One option might be to approach women producing large numbers of egg cells as a result of IVF. Other possibilities might be donation of IVF egg cells that had failed to fertilise or egg cells donated by women during gynaecological surgery. The first of these alternatives raises fresh moral questions, and none offer a real solution to the problem of scarcity (Health Council 1998).

The shortage of egg cells will clearly become even more pressing if SCNT does turn out to be a viable way of cultivating stem cells for cell therapy. A separate SCNT procedure will, after all, be required for each patient undergoing treatment. Though the efficacy of the procedure has significantly improved, many egg cells are still needed to produce a single patient-specific stem cell line via SCNT (Hwang 2005). However, it is not inconceivable that women might be more willing to act as donors if their egg cells are to be used to treat a loved one suffering from a serious disease than if they are to be used purely in scientific research.

Solving the scarcity problem by allowing women to sell ripe egg cells for vast sums, as happens in the United States and other countries, is not regarded as a morally acceptable solution in the Netherlands and is prohibited by law. This approach would also make cell therapy applications of SCNT so expensive as to preclude its general availability.

4 'Embryo-saving' alternatives?

This Section deals with the search for 'embryo-saving' sources of embryonic stem cells that could be used in autologous cell therapy. 'Embryo-saving' means that no human embryos have to be created in order to obtain the stem cells, thus enabling skirting of the related moral and legal discussion.

Isolating stem cells from surplus embryos is also embryo-saving in this sense, but this approach does not produce stem cells with a tissue type that is an exact match for the patient. The question is therefore whether methods (forms of SCNT or alternatives to it) can be devised that produce embryonic stem cells for autologous cell therapy without creating human embryos in the process.

A recurring theme in almost all alternatives that come up for discussion here is the idea that a non-viable embryo is not an embryo. To that extent, this search is being conducted not only with technical and scientific means, but also with conceptual and philosophical means. The first answer (SCNT does not produce embryos) is itself based purely on this approach.

Clonotes

Though other mammals that developed from SCNT embryos were born after Dolly, they appear to be the exceptions. Most embryos die, but in most cases where an embryo does survive to birth the animal was found to have severe abnormalities related to faulty gene expression (Cibelli 2002a). It would seem that 'clones that survive to birth merely represent the least abnormal animals' (Jaenisch 2004). It has been demonstrated that these findings cannot be dismissed as 'teething problems' with reproductive cloning. Rather, they seem to indicate a possibly insurmountable biological barrier: the failure to reactivate essential embryonic genes that are marked as 'switched off' in the transplanted cell (Jaenisch 2003).

Some authors have recently concluded from this that it is incorrect to say that an SCNT embryo has the potential, just like an IVF embryo, to develop into a human being (Jaenisch 2004, McHugh 2004a, Trounson 2002). By implication, this would remove the right to protection conferred on human embryos and would open up the possibility of using these 'products of SCNT' (Jaenisch 2004) as sources of transplant material without further discussion of whether human embryos can be created for research or therapy. A shift in terminology has also been suggested: these entities should be called 'clonotes' rather than 'zygotes' or 'embryos' (McHugh 2004a). 'We should use zygotes for babies, clonotes for cells' (McHugh 2004b).

However, many IVF embryos are also lost *in vitro* or following implantation, which can often be attributed to chromosomal abnormalities. This means that the difference in viability between IVF and SCNT embryos is, at most, a question of degree. And how important is it to the debate as to the status of the embryo that all kinds of serious health problems are likely when an SCNT embryo does develop into a child ('reproductive cloning')? Do 'potentially sick human beings' have a different moral or legal status from 'potential human beings'? It would seem difficult to uphold such an argument.

Cybrids

'Interspecies SCNT' involves transplanting a human somatic cell nucleus into a denucleated animal egg cell. There are two reasons for considering this procedure. First, it has been argued that this technique would probably not create human embryos, avoiding the issue of the moral and legal acceptability of the technique (Chang 2004, Solter 2003). Second, this would free SCNT from dependence on human donor egg cells. Of course, both advantages would only apply if the procedure delivered a usable source of human embryonic stem cells that were safe to use in therapeutic applications.

Little research has been carried out into this possibility so far, and the results have generally been disappointing. It is true that Chinese scientists recently reported that they had succeeded in obtaining human embryonic stem cells from embryos produced by transplanting

human cell nuclei into denucleated rabbit cells (Chen 2003), but doubt has been cast on whether these claims are fully justified (Solter 2003). No evidence has yet been produced showing these cells to have all the properties needed for therapeutic use of embryonic stem cells.

The safety of the procedure relates to the possible risk of cross-infections. The chance of cross-infection is probably low, as the technique does not make use of the nucleus of the animal egg cell (where animal viruses might be found). More clarity is needed on this issue before therapeutic use of embryonic stem cells obtained via interspecies SCNT can be considered. Of course, this proviso does not apply to fundamental scientific research.

Assuming that interspecies SCNT can be a useable and safe source of stem cells, this proposal raises two issues (De Wert 2001). First, are the embryos created by this process human or not? We need to consider the hybrid, or more accurately 'cybrid', nature of such constructs: the nucleus of one cell-type combined with the cytoplasm of another (Solter 2003). Does the fact that part of the genetic material of a human-animal *cybrid* of this kind is of animal origin mean that we cannot regard it as a *human* embryo? One objection to this argument is that almost all the genetic material of such an embryo is derived from the nucleus of the human body cell used in the procedure (Lanza 1999, Health Council 2002, De Wert 2003). The animal input consists only of the cytoplasm with the mitochondrial DNA responsible for cellular energy balance (Health Council 2001).

Then we turn to the second question: if these human-animal *cybrids* have to be regarded as human, are they then also viable? Can these *cybrids* develop into human beings (with mitochondrial DNA of animal origin in all their cells)? If further (*in vitro* or animal) research shows that they are certainly not viable, then what is their ontological, moral and legal status? Some people consider that this raises the question as to whether they are actually *embryos*.

Embryo-like artefacts

Until it has been clearly established that *clonotes* and *cybrids* are definitely not viable, the moral implications of this for how they can be treated remain undecided. The approach described below is aimed at resolving this uncertainty. A technical adjustment to the SCNT process would allow embryos to be created that do not have the potential to develop into human beings. This approach, 'creation of non-viable embryo-like artefacts', was put forward as an option for further investigation in a recent report of the US *President's Council on Bioethics* (The President's Council 2004)[1].

Dr. Hurlbut, an ethicist who is a member of this council, has suggested that this might be achieved by deliberately introducing a mutation into the nucleus of the cell body used in SCNT.

1 A further 'White Paper' of the President's Council was published in May 2005, shortly after the Dutch original of this report went into print (The President's Council 2005). This provides a further discussion of 'alternative sources of human pluripotent stem cells', including the idea of creating embryo-like artefacts via SCNT and genetic modification referred to in this report.

He is thinking of a gene (cdx2) that is required immediately after the blastocyst stage (the stage at which stem cells can be harvested) to allow the placenta to form. If this gene is not correctly expressed, then the embryo will not be able to become implanted in the womb and so will not be able to develop into a human being. Dr. Hurlbut considers that a structure of this kind cannot really be regarded as an embryo and so can be created and then emptied without any objections being raised (Hurlbut 2004, Hurlbut 2005).

The scientific response to this suggestion has been divided. Dr. Melton, a biologist, raises the question of whether a genetic mutation of this kind has the same effect on human embryos as in mice, and wonders whether it would be possible to obtain useable stem cells from the artefacts produced. The energy and resources needed to investigate this aspect would be taken away from really significant research, and it is doubtful whether this approach would satisfy those who are opposed to research on human stem cells (Melton 2004). Others consider that it is worth the difficulty of giving it a try (Ready 2005).

Parthenotes

Parthenogenesis involves chemically stimulating an unfertilised egg cell to transform it into a diploid cell. This produces an embryo-like entity with two identical sets of maternal chromosomes. This process does not involve fertilisation or cloning. It is thus an alternative to SCNT rather than a variant of it. Of course, the 'uniparental embryos' or 'parthenotes' are female. They are also not viable, as no extra-embryonic tissue needed for implantation and further growth is created. However, parthenotes could perhaps be used as a source of embryonic stem cells.

There has in the meantime been success in obtaining parthenogenetic 'embryos' from research on mice and apes (Boediono 1999; Cibelli 2002b). These were shown to have the ability to develop into blastocysts, and researchers have succeeded in obtaining cell lines that do not appear to differ from cell lines from embryos produced by fertilisation. However, initial attempts to obtain embryonic stem cells from human parthenotes failed (Cibelli 2002b). Furthermore, this method would only produce cell material matching the tissue type of the woman from whom the egg cell was taken.

It has been suggested that parthenotes may not be human embryos as they have only 'partial generative potential' (Hurlbut 2004, Jochemsen 2004, PCB 2004). However, another argument is that parthenotes should be regarded as non-viable embryos with a moral status that remains to be determined (De Wert 2003).

Direct reprogramming

Another alternative to SCNT, in which there has been interest for some time, is a technique known as direct reprogramming. The aim of this method is to develop pluripotent cells (the equivalent of embryonic stem cells) from somatic cells, without having to create an embryo as an intermediate

stage. This procedure is, in view of the advantages thought to be associated with it, regarded as *the* alternative for the future, (De Wert 2004, Trounson 2002). As with 'therapeutic cloning' via SCNT, this technique should produce matching tissue type transplant material for autologous cell therapy, thereby avoiding rejection. As no egg cells are needed for direct reprogramming and no embryos are produced, the moral objections raised against SCNT do not arise with this alternative.

But work on direct reprogramming is still in the very early stages and much more research is required. A first line of approach is trying to understand how (in SCNT) the denucleated egg cell or substances in the ooplasma (the cytoplasm of the egg cell) reprogramme the somatic cell nucleus. Once we know what mechanisms and substances are involved, we can try to imitate this in the laboratory via chemical induction. Much of this research can be conducted using animal material. However, species-specific differences mean that the question cannot be avoided of whether, and if so when, this research may need to be repeated on humans, creating *human* embryos via SCNT. In other words, this embryo-saving alternative can only be developed by means of research in which not only animal but also human embryos are created. It seems that this approach cannot, at least at this stage, help us get around the question of whether this is acceptable.

Another line of investigation might, indeed, allow this. This approach is looking into the possibility of direct reprogramming by transplanting a somatic cell nucleus (SCNT) into a human embryonic stem cell (Tada 2001; Do 2004). It appears that embryonic stem cells are capable of (at least partially) reprogramming somatic cells. This alternative would be embryo-saving (as embryonic stem cells rather than embryos are created) and also 'female-friendly'.

5 'Female-friendly' alternatives?

Some of the procedures outlined above would be both 'embryo-saving' and 'female-friendly', as they would not require egg cell donors. The approaches falling into this category are interspecies SCNT, parthenogenesis (where the patient's own egg cells are used) and direct reprogramming. However, two other options should be considered as well.

Unripe egg cells

Despite improvements, hormone stimulation carried out to obtain ripe egg cells is still the most burdensome and risky part of IVF treatment. This could change if *in vitro* maturation (IVM) can be performed to ripen unripe egg cells outside a woman's body (Health Council 1998).

Though some babies have been born following IVM, there has not yet been a breakthrough in this field (Hovatta 2004, Picton 2003). IVM embryos seem to particularly lack sufficient capability to develop. Furthermore, findings from animal research also raise concerns as to the possible health risks to the offspring (Health Council 1998, Tesarik 1996). However, this is not necessarily a barrier

to the use of IVM to obtain egg cells for SCNT, as it would, after all, not be a reproductive method.

IVM can currently only be carried out on egg cells that are fully grown (Picton 2003). In order to obtain egg cells for further ripening for use in SCNT, it would still be necessary to ask women if they are willing to donate egg cells (via vaginal puncture). The procedure would be much less burdensome and risky if this meant that hormone stimulation were no longer needed. If it is possible to grow and ripen human egg cells *in vitro* at a much earlier stage of development (primordial follicles), then this would open up other sources of egg cells for use in SCNT (such as ovaries removed during surgery or taken from deceased women or girls, or from aborted foetuses) (De Wert 1993). It is widely agreed that egg cells of this kind cannot be used for reproduction, but that is also not the intention here. To be acceptable, the use of these sources is of course dependent on the tissues being donated for scientific or therapeutic purposes in accordance with the current regulations.

The recent discovery that the ovaries of mice contain germ stem cells that can develop new follicles with egg cells even after the animals are born (Johnson 2004) has led to speculation that similar cells may exist in human ovaries (Spradling 2004). Following on from this, it has been suggested that isolating these germ stem cells could be a first step towards the mass production of egg cells for SCNT (Kadereit 2004).

Egg cells from embryonic stem cells

A number of research teams have recently reported that embryonic mouse stem cells can produce primordial germ cells that subsequently developed haploid gametes. This approach was used to obtain both egg cells (Hübner 2003) and sperm cells (Toyooka 2003, Geijsen 2003). Further work is needed to ascertain whether these are fully functional gametes that can develop into healthy new individuals after fertilisation. For the time being, this discovery would seem to be more important in terms of fundamental research aimed at reaching a better understanding of how gametes are formed (gametogenesis) in mammals. However, both the scientists involved and other commentators have already speculated as to possible applications in humans.

If it turns out that human egg cells can also be cultured from embryonic stem cells, then we may first of all think of how this can be used for SCNT (Solter 2003, Testa 2004). It would mean that human egg cell donors would no longer be needed for this procedure. The embryonic stem cells needed to culture egg cells could to a large extent be obtained from stem cell lines produced from donated surplus IVF embryos, and so the problem of a shortage of egg cells for SCNT would no longer exist. Furthermore, at least in mice, both female and male stem cells can be used to grow egg cells (Hübner 2003).

SCNT embryos produced using an egg cell cultured from embryonic stem cells may not be viable. They do not need to be for scientific or therapeutic applications. It is sufficient for them to be able

to develop to the blastocyst stage so that stem cells can be obtained from them and used in therapy. The difference between the stem cells at the start and end of the procedure is that SCNT makes the cells match the tissue type of the patient for whom autologous cell material is being developed. At a hearing of the President's Council on Bioethics, the American scientist Dr. Jaenisch (a member of the council) was optimistic about this line of work (Jaenisch 2003): 'It seems that technical issues, not fundamental biological barriers, need to be overcome so that transplantation therapy can be carried out without the use of human oocytes'.

6 New moral questions

The foregoing summary shows that various routes are being followed to find morally acceptable (or less controversial) variants of, or alternatives to, SCNT. If these procedures no longer require the creation or use of human embryos, then this would certainly represent a moral gain, even if only because research in this field and possible future applications would no longer be open to objections on the grounds that human embryos are deserving of protection. This would also bring more balance into the debate on the relative merits of further research into embryonic and adult stem cells (Solter 2003). The search for methods that do not require women to donate ripe egg cells is important not only because of the burdens and risks to which egg cell donors are unavoidably exposed, but also because of the shortage of egg cells that would otherwise present a barrier to the application of the technology. However, our summary of the two-pronged search raises fresh normative questions that are briefly addressed below.

The status of non-viable embryos

The idea that ties all the aforementioned 'embryo-saving' proposals together (apart from 'direct reprogramming') is that SCNT (or parthenogenesis) can be morally acceptable if the embryos created are not viable. The question of whether the non-viability of an embryo has consequences as to the protection it deserves (and if so, what these consequences are) is clearly important to the moral analysis of the proposals.

If it is concluded that non-viable embryos deserve a lesser degree of protection, then the principle of subsidiarity would imply that procedures producing such embryos should be chosen where possible. Hurlbut's idea of deliberately inducing non-viability by means of a genetic modification also deserves closer consideration in this context. However, the debate on the moral status of non-viable embryos must not be resolved simply at the level of the definition. This is the case if the argument runs: non-viable, therefore not an embryo, therefore not deserving of protection.

The report of the debate in the US President's Council seems to show that at least some members of the council find this reasoning attractive (Zucker 2004)[1]. The reaction of Dr. Kass, the chairman of

1 In the President's Council's 'White Paper' of May 2005 (see previous footnote), it is said that 'most of us believe the proposal offers enough promise to justify animal experimentation, both to offer proof of feasibility and utility and to get evidence bearing on some of the ethical issues' (The President's Council 2005).

the council, to Dr. Hurlbut's idea, is illustrative of this. His comment on the 'product' resulting from this combination of genetic modification and SCNT is:

> It would simulate certain organic activities, in the sense that there would be cell division, but it would have been engineered in such a way that you couldn't — if you understood what you were doing and what you have done, you could not call it a living human embryo. It would be embryo-like only in the sense that it went through certain stages of cell division but it would not be embryonic in the sense that it had no — it was incapable ab initio of being embryonic in the sense that it is pointed toward and developing — it is not a being to begin with, with that kind of future.

Mr. Doerflinger, the secretary of the American bishops' conference, was much less positive (Zucker 2004). Knowing that an embryo that started to develop normally will not survive because of a genetic defect has no consequences in terms of its ontological status under Roman Catholic doctrine (it is still an embryo) and so, as from this perspective the embryo must be regarded as a person, also has no consequences in terms of its moral status. The degree of protection that human persons deserve does not, after all, depend on how much further they can develop. An adult person who is inevitably going to develop Huntington's disease at around the age of forty and to die from this disease as a result of a genetic defect that occurred at conception is not therefore less deserving of protection than someone with a full life expectancy.

This reaction shows why the debate is being conducted by Hurlbut and others (Jaenisch, McHugh) in terms of the definition, rather than on the issue of whether non-viability has consequences for the moral status of human embryos. Those who consider that pre-implantation embryos must be regarded as persons and are thus deserving of complete protection will always have to answer 'no' to the latter question. That is not the case if such embryos are regarded as 'deserving of limited protection', but this approach already sees SCNT as acceptable. The aim of Hurlbut's suggested definition is to enable proponents of 'full protection' to accept SCNT while maintaining their view that human embryos cannot be used or created for research or therapy (Hurlbut 2005).

In a recent Dutch publication, some supporters of that view indicated that, like Doerflinger, they would not be won over so easily. They consider that SCNT (and similar techniques) could be acceptable only if it is certain that the artefacts produced cannot be regarded even as 'defective embryos'. Further animal research must first be carried out to rule out the possibility of more than limited embryonic development. Parthenotes or human-animal cybrids are considered as possible examples (Jochemsen 2004).

All in all, the search for embryo-saving variants of (or alternatives to) SCNT raises a new debate on the question of what exactly we mean by a (human) embryo and why we consider that human embryos are deserving of (greater or lesser) protection. The idea that non-viable human embryos are not embryos is, at least, counter-intuitive. This is clear from the awkward designations used, such as 'embryo-like artefacts' (PCB 2004), 'limited biological entities' (Hurlbut 2004),

'products of SCNT' (Jaenisch 2004) and phrases such as 'embryos that (...) cannot be regarded as embryos within the meaning of the Embryos Act' (HWS 2004).

A broader definition does not necessarily imply that non-viable embryos should enjoy the same degree of protection as embryos that do have the capacity to develop into human beings (De Wert 2003). But a broader definition of this kind does appear to be necessary in order to even raise the question of whether the former category of embryos deserves protection, and if so to what extent, in the context of a moral (and legal) analysis.

Egg cells from embryonic stem cells: for reproduction as well?

If it is possible to create egg cells from embryonic stem cells for purposes of research and therapy, can these then also be used for reproduction? Here, one could think of helping people who do not (or do no longer) produce functional gametes of their own still to have their own genetic offspring. As we first need a much better understanding of the efficacy and safety of reproduction with gametes of this type, reproductive applications are at present an entirely speculative scenario. It should be borne in mind that it has so far only proved possible to obtain cultured gametes from embryonic stem cells in mice. But as Testa (a biologist) and Harris (an ethicist) remark: 'Precisely because the technology is not yet within immediate reach, we believe it is timely to start developing a bioethical and legal discourse' (Testa 2004).

A reproductive method based on SCNT would involve the creation of an individual's own genetic sperm or egg cells and then using them together with the partner's gametes in a normal IVF or ICSI procedure. Although SCNT is involved, this is not reproductive cloning. If the procedure works correctly, then it will result in a child whose genetic make-up is a combination of that of *both* partners, just as in natural reproduction. The use of this procedure would obviate the need for reproduction with donor gametes for individuals who currently have to resort to this method as a result of fertility problems. It would always be possible, after all, to culture gametes from the concerned individuals, and this technique would therefore represent a major step forward in assisted reproduction.

It is quite correct that now is the time to start thinking about this possibility, even though it is still speculative. The possible reproductive applications of gametes obtained via SCNT cannot, after all, be simply placed within the well-known confines of human reproduction and the limits set on it by nature (Newson 2005). This route would allow male homosexual couples to have a child bearing the genetic make-up of both partners, although they would still need a surrogate mother. Testa & Harris thus see a challenge in this to our views on reproduction and parenthood:

> The possibility of an all male or all female couple's being able to have a child sharing the genetic make-up of both parents in virtually the same way as for heterosexual couples is thought-provoking and can be used as a lens through which to discern our attitudes toward parenting and the family, as well as our notions of what is 'natural'(Testa 2004).

This also applies to the fact that reproduction using egg cells obtained via SCNT would not be limited by the natural upper limit to the age at which women can bear children. The technique would allow functional egg cells to be obtained at any age. Other commentators see still more far-reaching possibilities: a man could use a surrogate mother to produce a child of which he is genetically both the father and the mother (Newson 2005).

Finally, bringing us back to the key topic of this report, we come to the question of how to regard the use of SCNT as an intermediate stage in a technique deliberately aimed at reproduction (where embryos are created for use as a source of gametes to be used in reproduction) in the light of the debate on the acceptability of creating embryos for purposes other than pregnancy. It is true that pregnancy would be the objective, but none of the embryos created via SCNT would develop into a human being.

The same question was raised in the opinion on *Nuclear transplantation in cases of mutations in mitochondrial DNA* (Health Council 2001). Responding to this opinion, the Minister stated that in her view 'this procedure did not represent an unacceptable infringement of respect for human life' as 'the most important element of the embryo (...) is retained, i.e. the nucleus that contains the inherited properties that help determine the development of specific individual characteristics' (Lower House 2001). The question is, doesn't this formulation reduce the embryo to the genetic information that it contains? And how does this then differ from any other human cell and the information contained in its nucleus?

7 New legal issues

In order to seriously address the question of the moral status of non-viable embryos, as argued above, embryos would have to be defined in terms that do not preclude non-viable embryos being regarded as embryos. This also applies to the matter of the legal status of such embryos in the light of the definition in Section 1c of the Embryos Act ('cell or collection of cells with the potential to develop into a human being'). As many IVF embryos are non-viable as a result of chromosomal abnormalities, this legal definition is, as has already been pointed out, too narrow. Could the legislator have intended to exclude these non-viable embryos from the law? It is hard to imagine that this could be the case (De Wert 2001, Dute 2003).

The legal definition is too narrow

The current legal definition leaves open the possibility of non-viable embryos being subjected to interventions that may be undesirable, but against which no objections can be raised on the grounds of the Embryos Act.

An intervention modelled after Hurlbut's suggestion (if technically feasible) would simply sidestep the prohibition on creating human embryos for purposes other than pregnancy (Section 24a); after all, this procedure would not create cells with the potential to develop into human beings, and so would

not create embryos as understood by the law. The fact that this procedure involves germ line modification is not a barrier either, as the relevant prohibition (in Section 24g) is limited to 'human germ line cells with wich a pregnancy is to be induced'. That is not the intention here, as the procedure is to be used to obtain (autologous) stem cells for cell therapy.

An essential requirement is, of course, that this procedure does indeed not produce viable embryos. But suppose that before this can be definitely established, further research is needed in which 'SCNT products' are created that may indeed be viable (Melton 2004). Does this research contravene Section 24a or not? What are the legal implications of such uncertainty? The same issue arises in the debate on variants such as interspecies SCNT (De Wert 2004). It has been pointed out here that human-animal cybrids must be regarded as human embryos from a moral and legal standpoint so long as there remains uncertainty as to their potential for development (Jochemsen 2004, Jones 2005). Surprisingly, the present government appears to reverse the burden of proof (HWS 2004):

> (...) the government assumes, unless evidence to the contrary is found, that embryos produced following the transplant of human cell nuclei into denucleated animal egg cells (...) are no longer viable at an early stage of development, and that they therefore do not have the capacity to develop into human beings and so cannot be regarded as embryos under the Embryos Act.

A further implication of the prohibition in Section 24a not being applicable to the deliberate creation of non-viable embryos as a result of the current definition is that if this method can be used to obtain stem cells that are useable in cell therapy, then the subsidiarity principle (as laid down in Section 10b) would require that surplus embryos no longer be used to isolate embryonic stem cells. This is because the SCNT route is less invasive, provided that it does not create embryos as defined by the Embryos Act.

Further to this, the question arises of whether the debate on lifting the prohibition in Section 24a has lost its relevance. As far as SCNT is concerned, both in respect of possible future therapeutic applications ('therapeutic cloning') and fundamental scientific research, this prohibition does not seem to present a barrier so long as the procedure does not create viable embryos.

One initial counter-argument to this is that the implications for SCNT are not the only reason to discuss the desirability of lifting the ban. The creation of embryos may be desirable for other forms of research, including investigations into the safety of IVF and other new reproductive techniques (Health Council 1998, De Rycke 2002). But the key point at issue is that the proposed 'solution' sidesteps the normative questions that arise here. The argument that these embryos are not embryos within the meaning of the law is also not a satisfactory answer from a legal perspective to the question of whether it is acceptable to create non-viable embryos.

The legal definition is too broad

The present definition also raises yet another problem. The phrase 'the capacity to develop into a human being' also appears to include too much. The definition is not only too narrow, but perhaps also too broad. After all, if every cell with that potential is an embryo, can we still assert that embryonic stem cells are not embryos? These cells are pluripotent, but are not capable of forming a placenta. Does that mean that they do not have the potential to develop into human beings? Researchers have succeeded in producing offspring from the embryonic stem cells of mice by injecting the cells into an abnormal embryo that only has the ability to form a placenta (Nagy 1993). If we assume that it would be possible by artificial means to achieve implantation of human embryonic stem cells as well, then should we regard them as embryos too?

The same question arises in connection with biopsies of embryonic cells (blastomeres) taken for genetic testing in the context of pre-implantation genetic diagnosis (PGD). They are (probably) incapable of developing into human beings without assistance (Health Council 1998), but may be able to do so with assistance. The question is therefore whether the definition in the Embryos Act implies that every cell or group of cells that could produce a human being as a result of the application of advanced technology should be regarded as an embryo. It has been pointed out that an 'inclusive embryo definition' such as this would have the absurd consequence of considering every body cell to be an embryo insofar as SCNT can create a viable embryo from them (De Wert 2001).

Should this consequence be dismissed? Could it be ruled out by interpreting the 'capacity to develop into a human being' as what was earlier referred to (in Section 1.2) as 'active potentiality'? This would mean understanding the 'potential' referred to in the law as an inherent tendency to fulfil an intrinsic purpose. If so, the potential of an embryo to develop into a human being is indeed of a completely different order than the 'capacity' to be manipulated in that direction that might be attributed to somatic cells or even to human DNA. This route, though, does not offer a solution to the problem.

Leaving aside the question of whether that interpretation of 'potentiality' (which harks back to a pre-modern understanding of causality) (Melton 2004) can be upheld, the issue here is really that nothing stands in the way of interpreting the legal definition in terms of 'passive potentiality'. The boundaries of the definition therefore continue to pose a problem.

An alternative definition could on the one hand include non-viable embryos and on the other hand be sufficiently clearly differentiated from the position that every human cell must, in fact, be regarded as an embryo. The following formulation is an attempt at such a definition: 'the fertilised oocyte, or any other functionally equivalent cell, and the whole of cells that develops from it prior to birth'.

8 Agenda points

— The developments discussed in this report show the need for a closer analysis of the moral status of non-viable human embryos. Reducing the debate to the level of the definition (not viable, therefore not an embryo, therefore not deserving of protection) is undesirable.
— The question of whether the legal definition of an embryo in Section 1c of the Embryos Act is adequate in the light of scientific progress should be given specific attention in the upcoming review of the law.
— The search for morally unobjectionable sources of embryonic stem cells discussed in this report does not render the debate on whether the prohibition in Section 24a should be lifted superfluous. In fact, it highlights the urgency of that debate.
— If it does turn out to be possible to create gametes from embryonic stem cells, then this would also be a significant breakthrough in moral terms. SCNT could then be carried out without the use of egg cell donors. But a pro-active moral analysis must also consider the possible reproductive implications of such a technique becoming available.

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Appendix 1

Standing Committee on Medical Ethics and Health Law

(Beraadsgroep Gezondheidsethiek en Gezondheidsrecht)

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prof. M de Visser, vice-president of the Health Council of the Netherlands; Health Council, The Hague
prof. GMWR de Wert, professor of biomedical ethics; Institute of Health Ethics, Maastricht University
prof. MA Verkerk, professor of medical ethics; University Medical Centre, Groningen
prof. DL Willems, professor of medical ethics; Academic Medical Centre, University of Amsterdam
A Bood; Health Council of the Netherlands, The Hague, scientific secretary
dr WJ Dondorp; Health Council of the Netherlands, The Hague, scientific secretary

Appendix 2

Relevant sections of the Dutch Embryos Act[1]

In force since 1 September 2002

Section 1

In this Act the following words shall have the following meanings:
(...)
c. embryo: a cell or a complex of cells with the capacity to develop into a human being;
(...)

Section 9

1. Adults who are capable of making a reasonable assessment of their interests in this regard may make their gametes available for the creation of embryos specifically for
a. culturing embryonic cells intended for implantation in humans where this can only be achieved using cells from specifically created embryos;
b. carrying out research using those embryos that is permissible under this Act.
2. (...)

Section 11

Carrying out research with embryos created specifically for this purpose is prohibited. This prohibition shall not apply to research which is reasonably likely to lead to new insights in the fields of infertility, artificial reproduction techniques, hereditary or congenital diseases or transplant medicine, and which can only be performed by making use of embryos as referred to in the first sentence.

Section 24

The following procedures are prohibited:
a. creating an embryo specifically for research purposes or for purposes other than the induction of a pregnancy and using such an embryo in research or for purposes other than the induction of a pregnancy;

1 Translation: Ministry of Health, Welfare and Sports, The Hague, 2002. With regard to section 9, 11 and 24(b) see also section 33, subsection 1; with regard to section 24(a) see also section 33, subsection 2.

b. creating an embryo specifically and using such an embryo for purposes other than the induction of a pregnancy or the purposes for which it may be made available pursuant to Section 9, subsection 1;
(...)
g. intentionally modifying the genetic material of the nucleus of human germ line cells with which a pregnancy is to be induced;
(...)

Section 33

1. This Act shall enter into force on a date to be determined by Royal Decree, which may differ for the different sections or parts thereof, on the understanding that Sections 9, 11 and 24(b) shall enter into force on the date referred to in subsection 2.
2. Section 24(a) shall lapse on a date to be determined by Royal Decree. The recommendation of this Decree shall take place at most five years after the date on which that part of the section enters into force. (...)