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Second interim report

of the Study Commission on the Law and Ethics of Modern Medicine*

Part report: Stem cell research

Translated by:
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* Set up by a decision of the German Bundestag on 24 March 2000 - Bundestag Printed paper 14/3011

Foreword

The interim report on stem cell research, submitted by the Study Commission on the Law and Ethics of Modern Medicine as instructed, contains a special feature: the section dealing with the ethical and legal appraisal of this research presents a detailed, comparative and impartial account of the various positions held both in society and within the Commission.

Clear identification is therefore possible of the areas in which consensus exists, where it ends and which questions, in view of the controversy surrounding them, require a decision to be taken. The various options for action are elaborated with premises and arguments, with a view to assisting individual members of the German Bundestag to reach their own decisions.

It is in the nature of ethicolegal judgements that they require general validity. However, no one has a monopoly on objective correctness. This is particularly the case where - as in research with human embryonic stem cells - high-ranking values of ethics and legal order have to be weighed against one another, because they come into conflict with each other.

With its interim report, the Study Commission provides Parliament not only with an overview of the prevailing status of relevant facts and discussion, but at the same time offers a method by which mutual trust, and possibly even consensus, may be achieved on the basis of respect for the decision of conscience of the other parties.

Particular thanks are due to the experts who provided specialist advice, adapting to parliamentary patterns of thought and debate, and to the secretariat and scientific advisors who have shown great dedication in the preparation of this report.

Berlin, 12 November 2001

Margot v. Renesse, MdB

Chairperson of the Study Commission on the

Law and Ethics of Modern Medicine

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CONTENTS

0 Introduction

The German Bundestag set up the Study Commission on the Law and Ethics of Modern Medicine on 24 March 2001, with the following particular instructions (BT Printed paper 14/3011):

- "To describe the situation relating to important current and future developments and the resulting problems in modern medical research, diagnostics and treatment, including the ethical, constitutional, social, legislative and political aspects;
- To investigate the relevant research practices and in particular to identify areas in which legal regulation is incomplete;
- To develop criteria for the limits of medical research, diagnostics and treatment and their application, within the unconditional dictates of respect for human dignity."

The Commission is to be involved in the preparation of decisions by the German Bundestag within the current parliamentary term.

On 5 July 2001, the German Bundestag took the decision to address the question of research in imported human and pluripotent embryonic stem cells within the current year, taking account of the view of the Study Commission (BT Printed paper 14/6551).

The Study Commission on the Law and Ethics of Modern Medicine is therefore presenting the section of its report dealing with stem cell research in the light of this decision. The text is based on preliminary work by the subject group "Applied medical research /new diagnostic and therapeutic methods" with the Study Commission on the Law and Ethics of Modern Medicine which, like the Commission itself, is made up of members of parliament and experts. Each member of the Commission had the opportunity at the draft stage to submit requests for additions and amendments. The Study Commission debated the draft text produced for this section of the report at two sessions on 5 and 12 November and adopted the report on 12 November 2001 with one dissenting vote and three abstentions.

The stem cell research report is the second interim report of the Study Commission on the Law and Ethics of Modern Medicine. In January 2001 the Commission presented an interim report as a subject report on “Protection of intellectual property in biotechnology" (BT Printed paper 14/5157).

1 Current status

Stem cells are cells that renew themselves by cell division and are capable of maturing into individual or several cell types (differentiation). They are therefore particularly suitable for cell and tissue replacement.

1.1 Scientific status

1.1.1 Historical and methodological development (derivation, proliferation and differentiation of stem cells)

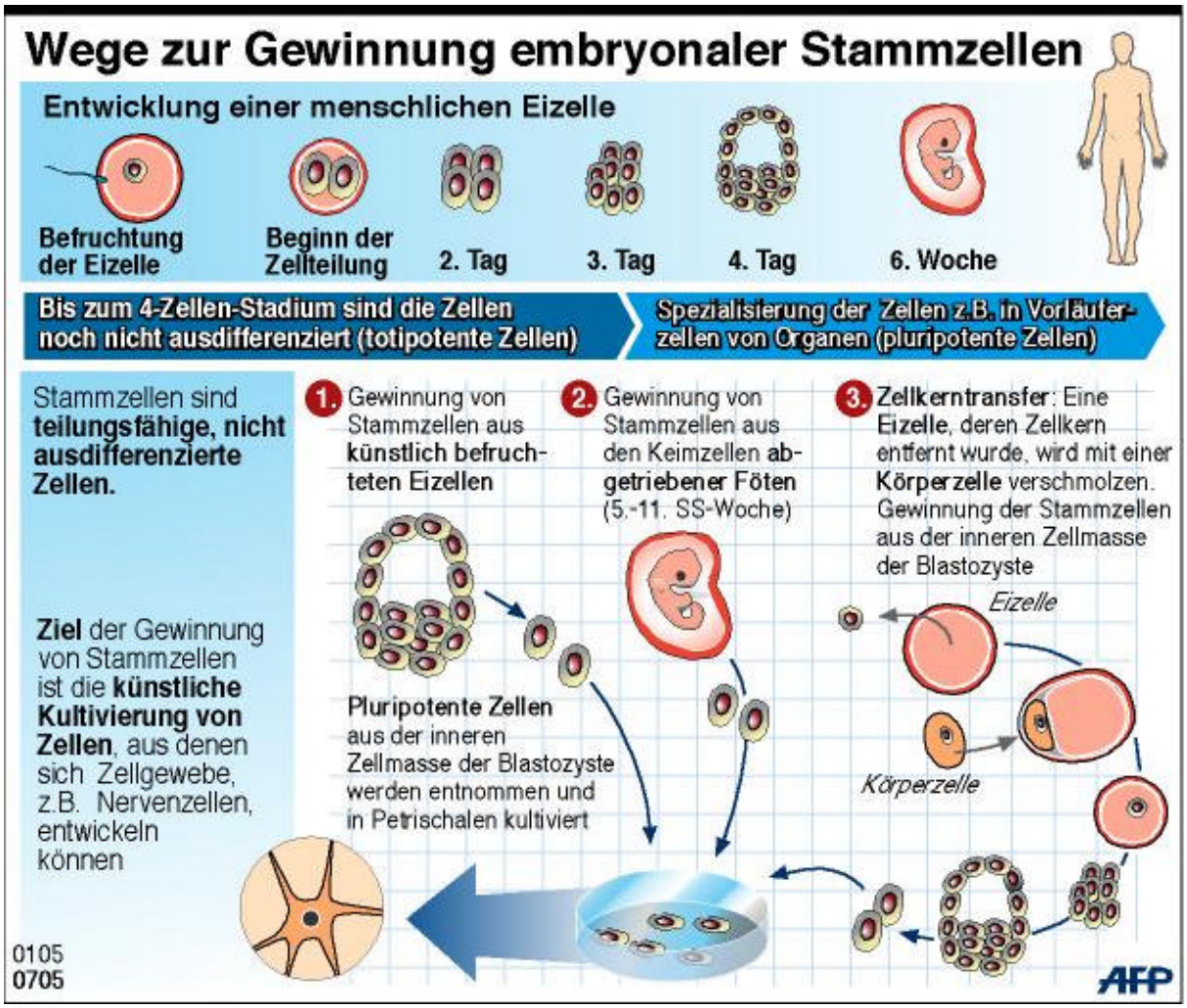

Figure 1[1]

[1] Totipotency is assumed up to approx. the 8-cell stage. The possibility that totipotency persists beyond this stage is currently under investigation. Cf. 1.1.1.6 Totipotency/Pluripotency.

Depending on their origin, a distinction is drawn between

- embryonic stem cells (ES cells) from embryos[2] derived from in-vitro fertilisation (IVF),
- embryonic stem cells produced by cell nuclear transfer,
- embryonic germ cells (EG cells) from terminations of pregnancy,
- neonatal stem cells from blood taken from the umbilical cord (cord blood) and
- adult or somatic stem cells that are tissue-specific and can be found into adulthood (AS cells).

1.1.1.1 Embryonic stem cells (ES cells) from IVF embryos

1.1.1.1.1 Derivation

Methods for the isolation of ES cells from mice have been known since the early 1980s.[3] Once the male and female pronuclei unite, cell division proceeds until, after approx. four days, the blastocyst stage (100 – 200 cells) is reached. The blastocysts have a diameter of around 100µm and consist of an outer cell layer and an inner cell mass. In the course of individual development the outer layer of cells, or trophoblast, will go on to form the fetal section of the placenta and parts of the fetal membranes, while the embryo and umbilical cord develop from the inner cell mass, the embryoblast. ES cells can be derived from the inner cell mass.

In mice, there are now a number of established cell lines that proliferate under the appropriate conditions in vitro and can be cultured indefinitely in the undifferentiated state. These cells can also be deep-frozen and stored for long periods. Around seven to eight cell lines[4] are used in research in mouse ES cells throughout the world, well over 90% of this work being carried out in five cell lines[5]. The characteristic properties of ES cells include:

- proliferation over an indefinite period in the undifferentiated state,
- stable, unchanged sets of chromosomes,
- spontaneous differentiation into various cells of all three germ layers in vivo and in vitro,
- potential differentiation into all cell types of the adult organism, including germ cells, after injection into foreign blastocysts.[6]

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[2] Embryos are defined as the early forms of human life up to the end of organogenesis, i.e. in the first three months of development. Embryonic stem cells are harvested at the blastocyst stage.
[3] Evans / Kaufman 1981; Martin 1981
[4] Verbal communication PD Dr. Wobus during the closed hearing on 23 April 2001.
[5] Deutsche Forschungsgemeinschaft 2001b, p. 4.
[6] Pera at al. 2000.

ES cells are further characterised by various other properties, e.g. certain molecules on the cell surface or a high nucleus-to-cytoplasm ratio.

In the early 1990s, cells with the characteristics of embryonic stem cells were also found in rats, sheep, cows, pigs and non-human primates. So far, however, it has been possible to identify all the above criteria only in the mouse. Nevertheless, the term ES cells will be used in this report to describe all these cells, since the designation has been adopted for these cells by both scientists and the public.

It first became possible to isolate and culture human embryonic stem cells in 1998.[7] The US National Institutes of Health (NIH) on their internet site report the existence of 64 genetically diverse ES cell lines which are now being produced by companies and university institutions in the USA, Sweden, India, Australia and Israel.[8] However, the number of cell lines and their quality has been called into question by the important American scientific organisation, the American Association for the Advancement of Science (AAAS). However, since no standards yet exist for the characterisation of ES cell lines, the NIH are forced to rely on information provided voluntarily by the companies or institutes concerned. No comparative investigations have yet been published with regard to ES cells of different origin. According to scientific publications, ES cell have so far been maintained in culture over more than 250 cell divisions, i.e. for more than eight months.[9]

For ethical reasons it is impossible to investigate whether human ES cells would be capable, after implantation into a uterus, of developing into a complete individual. Nor is it possible to investigate whether human ES cells, after being returned to another blastocyst, would take part in embryonic development and enter the germ line, as is the case with mouse ES cells.

With the methods used at present, the harvesting of ES cells results in the destruction of the blastocyst. However, it is conceivable that in the future more refined techniques could establish ES cell lines from individual embryoblast cells in a way that the preserves the viability of the embryo. Although this has been tried successfully, for example in mouse embryos, it is likely to remain medically unjustifiable in humans in the long term, in view of the unknown risk of injury, to use blastocysts from which cells have been removed in this way to bring about a pregnancy.[10]

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[7] Thomson et al. 1998.

[8] National Institutes of Health 2001b: The cell lines satisfy the criteria imposed by US President George W. Bush for those cells in which research may be conducted with US public funds:
the cell derivation process was initiated before 9.00 p.m. EDT on 9 August 2001;
informed consent was obtained from the couple from whom the embryo originated;
the cells were derived from an embryo created for reproductive purposes but no longer needed for this purpose;
there was no financial inducement to make the embryo available for research.

[9] Amit et al. 2000.

[10] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.

1.1.1.1.2 Replication and differentiation

Some experts are of the view that, at least for the purposes of basic research, small numbers of viable cell lines would be adequate, so that no further "consumption" of embryos would be required.[11] In order to establish these human ES cell lines, with the present state of the art, only a limited number of embryos would therefore be needed.[12] However, numerous researchers assume that the cell lines described to date in scientific publications will be by no means be adequate in view of their low potential for proliferation.[13] Human ES cells take 36 hours to double in number, compared to only 12 hours for mouse cells.[14]

Other experts consider it likely that a larger number of cell lines will be required for therapeutic use than in mice – possibly even 100 to 1000 – since slight differences n between the cell lines have been identified.[15] This does not take into account the need to use further embryos if, for purposes of cell and tissue replacement, cell lines with different tissue characteristics are required and are to be made available in ES cell banks. Testing for tissue compatibility before stem cells are transferred can help to prevent rejection of the cells by an immune reaction in the patients concerned. For this reason, the European Science Foundation speaks of cell banks containing 4000 ES cell lines.[16]

To derive differentiated cells from ES cells, these are cultured using growth factors. This results in an accumulation of what are known as embryoid bodies.[17] These are cell colonies which may contain derivatives of all three germ layers. Differentiation can be initiated by adding or removing certain growth and differentiation factors. In the mouse, much information is already available concerning the processes of regulating growth and differentiation. However, clear differences have already been identified between human ES cells and mouse ES cells with regard to the factors responsible for regulation, although a high differentiation potential is evident for human ES cells as well as for mouse cells.

One of the key problems in the derivation of differentiated cells from ES cells is purification. The purity of transplanted cells is crucial, since the smallest quantities of immature embryonic cells can lead after transplantation to the formation of undefined/unwanted cells foreign to the tissue or tumours (known as teratomas or teratocarcinomas).[18] Moreover, differentiation in cell

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[11] Verbal communication by Prof. Dr. Brüstle at the closed hearing on 23 April 2001.
[12] Wobus / Brüstle 2001.
[13] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.
[14] Amit et al. 2000.
[15] Melton 2001.
[16] European Science Foundation 2001.
[17] Recent findings indicate that ES cells, even without prior aggregation to embryoid bodies, can be developed efficiently into somatic cell types (Kawasaki et al. 2000, Wobus / Brüstle 2001).
[18] Verbal communication Prof. Dr. Brüstle at the closed hearing on 23 April 2001.

culture leads to a mixture of various cell types. The harvesting of cells of a defined type, however, is the prerequisite for possible therapeutic applications.

It has been possible to differentiate mouse ES cells in vitro to cartilage cells, epithelial cells, cells of the blood and nervous systems, insulin-producing cells and heart, skeletal or vascular muscle cells.[19] In ES cells from non-human primates, spontaneous differentiation into myocardial cells and neurones has been observed and also into cells of the endoderm and trophoblast[20.21] With regard to directed differentiation and the effect of various factors on ES cells from non-human primates and human ES cells, research is still at an early stage.

1.1.1.2 Cell nuclear transfer for the derivation of embryonic stem cells (ES cells)

1.1.1.2.1 Derivation

The transfer of a diploid cell nucleus into an enucleated, unfertilised egg cell allows asexual replication even in mammals. Dolly, the cloned sheep, provided the first evidence that this cell nucleus can also originate from adult somatic cells. Since then, offspring have also been created in cattle, goats, mice and pigs by this process of reproductive cloning.[22] The environment in the egg cell makes it possible to reprogram nuclei from differentiated somatic cells in such a way that a totipotent cell is produced.

In cloning experiments in animals, problems are frequently encountered during pregnancy (disturbances in placental development, increased abortion rates, fetal abnormalities) or severe damage to the health of the newborn animals.[23] One of the causes is suspected to be incomplete or defective reprogramming of the cell nuclei, leading to defective activation of genes relevant to development. Only in 1% to 5% of experiments does correct reprogramming appear to take place.[24] The acceleration of reprogramming, which in the formation of egg and sperm cells in the animal or human organism takes place over months or years, so that it occurs in vitro over a few minutes or hours may possibly result in incomplete reprogramming which may result in the above damage.[25]

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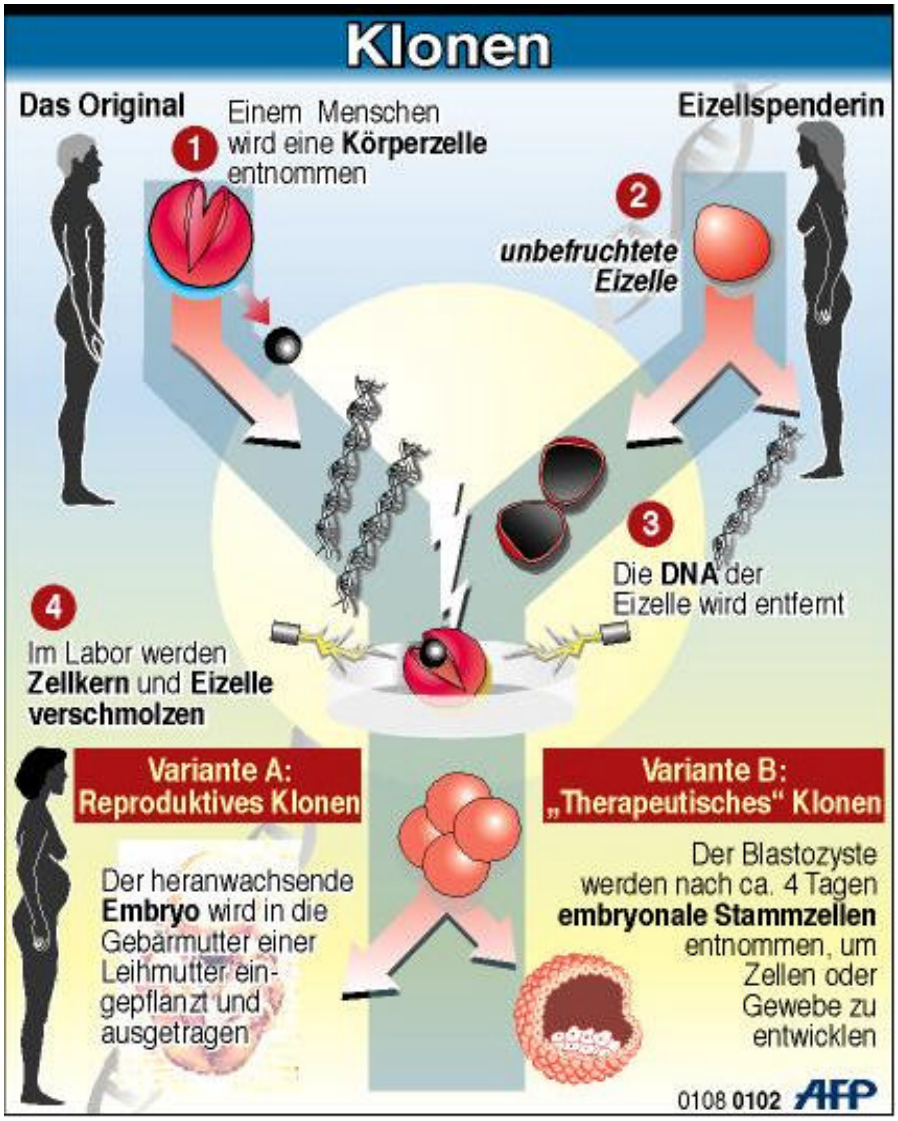
[19] Fuchs / Segre 2000; Odorico et al. 2001.
[20] The possibility of developing trophoblast cells distinguishes primate cells from those of the mouse and is interpreted by some as an indication that primate cells differ from mouse cells with regard to totipotency.
[21] Thompson / Marshall 1998.
[22] Wilmut at al. 1997; Wakayama et al. 1999; Bethauser at al. 2000; Polejaeva et al. 2000.
[23] Dolly, the cloned sheep, was the only animal born after 277 cell nuclear transfer procedures (Wilmut et al. 1997).
[24] Rideout et al. 2001.
[25] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.

Figure 2[26]



Cell nuclear transfer results in the creation of individuals whose nuclear genome is identical with the original cell but who also possess the mitochondrial DNA from the cell plasma.

Totipotent cells created by cell nuclear transfer, after their development to the blastocyst in vitro, may also be used as a basis for establishing ES cell lines. However, as with the creation of cloned animals, a large number of genetic and epigenetic defects must also be expected in the cell lines. The extent to which these cell lines could be used for cell and tissue replacement is therefore unclear. The establishment of ES cell lines is a more complicated and lengthy process, in view of the lower efficiency of cell nuclear transfer, than the use of "normal" mouse embryos.

[26] The method as shown here requires the use of a large number of egg cells.

The process has become known as "therapeutic" cloning to distinguish it from reproductive cloning, since it is hoped that use of the procedure in humans could result in the creation, from a somatic cell of a patient and an enucleated egg cell, of embryonic stem cells with the genetic characteristics of that patient for therapeutic purposes (autologous cells).

In order to reprogram the nuclei of somatic cells from patients, human egg cells would need to be used. Human egg cell donation, however, is associated not only with medical risks but also with ethical problems. Since estimates suggest that, even under favourable conditions, at least 280 human egg cells could be required to establish a single ES cell line by "therapeutic" cloning[27], egg cells of animal origin and enucleated ES cells or embryonic germ cells (EG cells[28)] have been discussed as possible alternative host cells for nuclear transplantation.[29] In September 2001 it was reported from China that at least 16 cell divisions took place after the transfer of cell nuclei from human skin cells into rabbit egg cells.[30] As early as 1999, human cell nuclei were transferred into egg cells from cows and pigs and cultured up to the 32-cell stage.[31]

Groups of cells produced in this way are chimeras with regard to their genetic material because, in addition to human nuclear DNA, they also contain mitochondrial DNA of animal origin.[32] It is uncertain whether the interaction of gene products of the nuclear genome and of the mitochondrial genome required for the building of mitochondria can take place in such cells and whether functional compatibility exists between the molecules of the different species present in the egg cell, which appears to be necessary for reprogramming.

The use of ES cells of embryonic germ cells (EG cells)[33] as host cells for nuclear transplantation would be conceivable if the factors necessary for reprogramming were identified. Clarification of the mechanisms involved in reprogramming and isolation of the necessary factors from egg cell plasma are therefore among the fundamental objectives of experiments in "therapeutic cloning". It is therefore impossible at this point to estimate how many such experiments in cloning will be necessary and to what extent findings obtained in other mammals can be extrapolated to humans.

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[27] Colman / Kind 2000.
[28] Cf. 1.1.1.3 Embryonic germ cells (EG cells).
[29] Solter et al. 1999; Gearhart et al. 2000.
[30] "Chinese genetic engineers cross human and animal" 2001; "At the limit between human and animal" 2001; "China finances the crossing of human cells with those of animals" 2001.
[31] Obermauer 2000.
[32] Wobus / Brüstle 2001.
[33] Cf. 1.1.1.3 Embryonic germ cells (EG cells).

1.1.1.2.2 Proliferation and differentiation

Little is known at present of the potential for proliferation and development (differentiation potential) of ES cells produced by cell nuclear transfer. ES cell lines produced by this method in the mouse have so far shown only limited ability to develop.[34]

1.1.1.3 Embryonic germ cells (EG cells) from terminations of pregnancy

1.1.1.3.1 Derivation

Embryonic germ cells (EG cells) can be harvested from the precursor cells of egg and sperm cells, known as primordial germ cells, in the late embryonic or early fetal stage[35].

Mouse EG cells, like ES cells, have a high proliferation and development potential: after injection into foreign blastocysts, EG cells, like ES cells, differentiate into all cell types of the adult organism, including germ cells. In cell culture, EG cells differentiate into a variety of specialised cell types of all three germ layers.

Human embryonic germ cells can be isolated from human embryos and fetuses at several weeks of age, following termination of pregnancy. The human EG cell lines described to date were derived from embryos or fetuses at 5 to 11 weeks of pregnancy.[36] Because of the variation in times at which pregnancies are terminated and since the embryo or fetus dies during the termination, harvesting of EG cells is more difficult than the isolation of ES cells. For technical reasons, e.g. because of insufficiently sterile conditions, it appears unlikely that suitable EG cell lines can be established from spontaneous abortions.[37]

1.1.1.3.2 Proliferation and differentiation

During the proliferation and differentiation of EG cells in the presence of certain factors, embryoid bodies are produced as with ES cells. The problems[38] described for ES cells in the purification of cells and harvesting of specific cell types are also encountered with EG cells.

Mouse EG cells, like ES cells, differentiate into a large number of specialised cell types such as heart, skeletal muscle and nerve cells.[39] However, mouse ES and EG cells appear to differentiate into particular cell types with varying degrees of efficiency.[40] Moreover, differences have been identified between certain mechanisms of gene regulation: during the

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[34] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.
[35] Cf. footnote 1
[36] Shamblott et al. 1998 / 2001
[37] Wobus / Brüstle 2001.
[38] Cf. 1.1.1.1.2 Proliferation and differentiation
[39] Rohwedel et al. 1996.
[40] Badura-Lotter 2000, p. 59.

development of an organism, individual parent alleles are selectively inactivated by a modification of DNA. In the germ cell precursors from which EG cells are produced, this process, known as imprinting, is missing. The question of whether the cells differentiated from EG cells are capable of fulfilling their normal function remains to be clarified. No investigations have been conducted to date. However, after mouse EG cells were used for cell nuclear transfer into enucleated cells, severe developmental anomalies were observed in the developing embryos.[41]

No detailed findings are yet available on the proliferation and development capabilities of human EG cells. The cells used to date show a capacity for proliferation inferior to that of ES cells, though their genetic activity exhibits a broad potential for development (differentiation potential).[42] Human EG cells can be stimulated to develop various tissue-specific markers that correspond to those of the cell precursors of the nervous system and of cutaneous, epithelial and vascular endothelial cells.[43]

It is impossible at present to say whether EG cells may provide an alternative to ES cells.

1.1.1.4 Neonatal stem cells from cord blood

1.1.1.4.1 Derivation

The harvesting of stem cells from cord blood directly after parturition has been practised for some years, in order to obtain haematopoietic stem cells as an alternative to bone marrow transplantation. Around 1,500 transplant procedures using neonatal stem cells have now been performed world-wide.[44]

Following delivery of the child, the umbilical cord is clamped and cord blood collected. The decision to divide the umbilical cord at a particularly early stage in those women for whom stem cells are to be harvested from the cord blood can occasionally be associated with disadvantages to the child.[45]

Within 24 hours of collection, cord blood is processed and deep frozen for long-term storage. Viral tests are performed with samples of the cord blood in order to exclude subsequent transmission with the transplanted material. The mothers are also tested for viruses such as HIV, hepatitis B and C. In addition, the cord blood is also subjected to tissue typing. A further

[41] Kato et al. 1999.
[42] Shamblott et al. 2001.
[43] Shamblott et al. 2001.
[44] Ordermann et al. 2000.
[45] Blood values for children whose umbilical cords were cut immediately after delivery differ from those cut at a later stage (Gordijn / Olthuis 2000).

blood sample is usually taken from the mother after a few months to check whether viral diseases are present which were not yet detectable at the time of delivery.

The use of somatic stem cells from cord blood offers a number of advantages: harvesting of the cells is practically risk-free for donors, the prevalence of transmissible viruses is low and cryopreservation allows the cells to be made available over a long period. Although stem cells are present in cord blood in high concentrations, the absolute number of cells is limited in view of the small quantity of cord blood. The quantities of usable blood are suitable for the treatment of children (bodyweight approx. 20 – 25 kg). The number of stem cells is frequently not sufficient to replace bone marrow transplantation in adults. However, patients with a weight of almost 100 kg have been successfully transplanted with neonatal stem cells.[46] Moreover, at least for bone marrow transplantation, only half the number of cells are required for transplantation with the patient's own cells (autologous transplantation) compared with allogeneic (heterologous) transplantation of donor cells.[47]

1.1.1.4.2 Proliferation and differentiation

The ability of neonatal stem cells to proliferate in cell culture is considerably superior to that of haematopoietic stem cells from bone marrow and peripheral blood (cf. the following section).[48]

It has now been shown that mesenchymal stem cells which differentiate, for example, into cartilage, bone, muscle, tendon or fat cells can also be obtained from human cord blood.[49] This differentiation can take place in accordance with the guidelines for Good Manufacturing Practice for medicinal products (GMP)[50] without the addition of substances of animal origin.

1.1.1.5 Adult stem cells (AS cells)

1.1.1.5.1 Derivation

Even in adult mammals, stem cells that renew themselves and are not yet finally differentiated exist for the regeneration of certain tissues. The best known examples are the haematopoietic stem cells found in the bone marrow, which are capable of differentiating into all blood cells. There are also adult stem cells in the liver, skin, hair, inner wall of the intestine and other tissues which frequently have to regenerate. Even in the lungs, retina and teeth and in tissues with low regenerative capability, such as the nervous system, the existence of such precursor

[46] Laporte et al. 1998.
[47] Wils 2000.
[48] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.
[49] Erices at al. 2000.
[50] Guideline of the Commission for determining the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for use in humans (91/356/EWG) dated 13.06.1991 (European Community 1991).

cells has been demonstrated.[51] Around 20 main types of adult stem cells have been discovered to date.[52]

The harvesting of such tissue-specific AS cells may be problematic, since the cells are present in organs like the heart, brain or pancreas and only in small numbers. Other researchers assume that the difficulties encountered in harvesting AS cells is due to lack of experience. However, it is suspected that the number of somatic stem cells decreases with age.[53]

The stem cells from bone marrow are relatively easily accessible. Allogeneic (heterologous) blood stem cells from bone marrow, however, have to be harvested in the operating theatre by puncturing the bone marrow under anaesthetic, resulting in a considerable physical and psychological burden for the donor. The harvesting of blood stem cells from peripheral blood (peripheral blood stem cell transplantation, PBST), which has now been used in clinical practice, promises to provide a solution. The formation and release of blood stem cells from the bone marrow into peripheral blood can be stimulated by the use of growth factors. The long term effects of the use of growth factors and other pharmacological manipulations (e.g. chemotherapy) for the formation and release of blood stem cells, however, have not yet been researched adequately so that this treatment is currently used only for the autologous harvesting of blood stem cells prior to myeloablative or myelosuppressive therapy. The use of growth factors in allogeneic stem cell donors is currently allowed only under clinical trial conditions after approval by the Ethics Committee responsible.

After liposuction in plastic surgery, mesenchymal stem cells have been harvested from fatty tissue which can differentiate into cartilage, bone, muscle or tendon cells.[54]

AS cells have also been isolated post mortem from the brain.[55] These cells were taken a few hours after death and it was found possible to stimulate them to differentiate and divide. However, they were not capable of indefinite proliferation, so that in this case they were described as precursor cells and not as stem cells.

On the basis of their biological characteristics, tissue-specific stem cells from embryos or fetuses are comparable with adult tissue-specific stem cells. Some human embryonic or fetal stem cells (e.g. neural stem cells) are capable of proliferation to a certain degree. The ability to develop has been demonstrated, for example, for human neural or pancreatic fetal stem cells.

By contrast with the harvesting of EG cells, several embryos or fetuses from simultaneous abortions are needed for the harvesting of tissue-specific stem cells.

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[51] Emura at al. 1997; Ahmad at al. 2000; Gronthos et al. 2000; Eriksson et al. 1998.
[52] Deutsche Forschungsgemeinschaft 2001b, p.9.
[53] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.
[54] Zuk et al. 2001.
[55] Palmer et al. 2001.

1.1.1.5.2 Proliferation and differentiation

If it is to be used therapeutically, the stem cell population must exhibit adequate ability to proliferate in cell culture. As a series of control mechanisms is provided in the body in order to prevent malignant degeneration of the stem cells, difficulties are expected with the proliferation of AS cells. On the other hand this characteristic of the cells also reduces the risk of tumour formation following therapeutic use.

The ability of haematopoietic stem cells to proliferate in vitro is very limited. By contrast, mesenchymal stem cells from bone marrow exhibit considerable proliferation potential and stem cells from cord blood and skin can be cultured considerably more readily than haematopoietic stem cells.

The potential of AS cells depends crucially on their ability to develop. For a long time it was assumed that tissue-specific AS cells were capable only of developing into their target tissue, but in recent years it has increasingly been found that differentiation into other cell types is also possible. Even without cell nuclear transfer, which leads to a complete reprogramming of differentiated somatic cells, tissue-specific AS cells can under certain conditions be made to mutate into a number of cells not within their usual development spectrum (transdifferentiation). Adult mouse neural stem cells, for example, have been found to differentiate into skeletal muscle, heart, lung, blood and skin after implantation at embryonic stages.[56] In the mouse, bone marrow stem cells are capable of developing not only into types of blood cells but also into liver, muscle and neuronal cells.[57] Muscle cells in turn can differentiate into blood cells.[58] Human haematopoietic stem cells are known to be capable of developing into liver cells after bone marrow transplantation.[59] Some experts therefore now suspect that stem cells from bone marrow may be capable of developing into any cell type.[60]

The mechanisms of differentiation of AS cells into specific cell types are unknown. Since the cell environment is of decisive importance in the development of cells, it is assumed that certain proteins are able to determine the development of cells into a cell type not within their development spectrum (transdifferentiation). It may even be possible to convert AS cells back to a pluripotent stage, as seen in ES cells (reprogramming[61]).[62] It has so far not been possible to control the processes of transdifferentiation or reprogramming.

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[56] Bjornson et al. 1999; Clarke at al. 2000; Krause et al. 2001.
[57] Ferrari et al. 1998; Petersen et al. 1999, Mezey 2000.
[58] Gussoni et al. 1999.
[59] Theise et al. 2000.
[60] Melton quoted in Vogel 2001.
[61] To distinguish this transformation of AS cells from the processes involved in cell nuclear transfer, the term “retrodifferentiation” is also used.
[62] Watt / Hogan 2000.

Whether a detailed investigation of the mechanisms involved in transdifferentiation and reprogramming can be conducted in AS cells themselves is uncertain. It is also difficult to judge whether clarification of the processes of differentiation of ES cells will play a decisive part in understanding the transdifferentiation procedure and to what extent animal experiments will provide the necessary basic information in this area.

Various companies have issued press reports of decisive progress made in the reprogramming of AS cells. Neonatal stem cells[63], bovine skin cells[64] and human T cells from the immune system[65] are reported to have been converted to a pluripotent state similar to that of ES cells. The experiments have not yet been published in scientific journals.

1.1.1.6 Totipotency / Pluripotency

Use of the terms totipotency and pluripotency in the scientific literature is inconsistent: in classical embryology, the totipotency of a cell is understood to mean the ability to develop into a complete individual. Pluripotent cells, however, in the context of classical embryology, are capable of developing into a variety of cells, tissues or organs but not into a complete individual. In research into mouse ES cells, however, totipotency is understood to mean the capacity, after injection into foreign blastocysts, to be involved in the formation of all tissues including those of the germ line.[66] Other definitions of totipotency include the capability of a cell to differentiate into all three embryonic germ layers or all cells types of an organism.[67]

Against the backdrop of the legal situation in Germany, special significance attaches to the potentiality of the human cells used in stem cell research, since the German Embryo Protection Act regards embryos and totipotent cells as legally equivalent. In this context, totipotency is understood in the classical embryology sense as the ability to form a complete being, i.e. an individual.

Since for ethical reasons the potentiality of individual human cells cannot be investigated empirically, the findings of experiments with animal embryos must be applied to humans.

Findings to date indicate that, during normal development of a human, the stage of totipotency is limited to the fertilised egg cell and the daughter cells arising during the initial stages of division. Many experts therefore rule out the possibility that ES or EG cells implanted into a uterus could continue to develop into an individual. ES and EG cells are therefore classed as pluripotent.[68]

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[63] Anthrogenesis Corporation (USA).
[64] PPL Therapeutics (Great Britain).
[65] Tristem (Great Britain)
[66] Beier 2000, p. 57 f.
[67] Badura-Lotter 2000, p. 60.
[68] Verbal communication from PD Dr. Wobus at closed hearing on 23 April 2001.

Individual experts, however, regard the idea that ES and EG cells are no longer totipotent as unproven. They are critical of the fact that the development potentials of the embryoblast cells from which ES cells are derived have not been systematically investigated. Investigations conducted in the USA in 1996, which indicated that ES cells from common marmosets are capable of developing a germ-layer-like structure in culture, are therefore being repeated to determine whether they are totipotent or pluripotent.[69]

Understanding of the concept of totipotency based on classical embryology is called into question by the availability of the technique of cell nuclear transfer since, under certain experimental conditions, even cell nuclei from adult tissues can be used to produce a cell with totipotency (reprogramming). In this case it is only the product of cell nuclear transfer that is to be defined as totipotent and not the original cell. With the reprogramming of AS cells the question also arises as to whether these reach the level of totipotency or whether they remain pluripotent.

It remains unclear whether it is technically possible to rule out formation of the complete organism while differentiation into specific cells or tissues remains a possibility.

1.1.2 Application and utilisation

Possibilities for the use of stem cells are at present limited to a few areas. Tissue-specific adult human stem cells are employed in individual therapeutic procedures and mouse ES cells are used to breed animals that serve as models of human disease.

1.1.2.1 Therapeutic application

The clinical use of stem cells is currently restricted to AS cells and neonatal stem cells, used within their tissue specificity. Increasingly, however, curative studies are being conducted outside the spectrum of tissue specificity.[70] No transdifferentiation or reprogramming is taking place.

Haematopoietic stem cells are being harvested from bone marrow and used for regeneration of the haematopoietic system after chemotherapy or radiotherapy in certain forms of cancer and autoimmune disease.

Mesenchymal stem cells also derived from bone marrow are capable of differentiating, for example, into cartilage, bone, muscle, tendon or fat cells. These stem cells are already being used in some hospitals for transplantation in diseases of the cartilage and bone.[71]

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[69] Thomson et al. 1996. The German Research Association (Deutsche Forschungsgemeinschaft) did not agree that a project to repeat this experiment should be taken forward within its specialised stem cell programme.
[70] Strauer et al. 2001.
[71] Bruder et al. 1994; Horwitz et al. 1999; Caplan et al. 2000.

Neonatal stem cells are used in the reconstruction of the immune system in place of bone marrow transplantation in children.

Stem cells from skin are being cultured in vitro and used to replace areas of skin damaged by burns.[72]

Epithelial stem cells from the cornea are transplanted for the treatment of certain diseases of the eye.[73]

In a curative study[74] in a 72-year-old patient, skeletal muscle was used to treat heart failure.[75] Since March 2001, six patients in Düsseldorf who had suffered a myocardial infarction have been treated with autologous stem cells, i.e. stem cells from their own bone marrow. One of the patients was found to have improved perfusion in the area of the infarct ten weeks after the treatment. The size of the area paralysed by the infarction was clearly reduced.[76] However, attention was drawn to the fact that regeneration processes of this kind are possible even with conventional methods of treatment and it is therefore not proven that the improvement is attributable to stem cell therapy.[77]

1.1.2.2 Mouse ES cells

Since mouse ES cells are capable, after injection into a foreign blastocyst, of colonising even the germ line, genetically modified cells can be used to produce animals in which certain genes are modified (transgenic animals) or abolished (knock-out animals). These animals can help to identify an association between a gene and a particular genetic function or a disease and are used as models for the corresponding human diseases.

1.1.3 Expected future developments

The use of stem cells in medical research and treatment is being considered in a number of different areas.

1.1.3.1 Stem cells in basic research

The complex processes involved in the differentiation of tissues and organs are still largely not understood. Basic research – in particular with ES cells – should make a considerable

[72] Fuchs / Segre 2000.
[73] Tsubota et al. 1999.
[74] The term curative study is used here in the legal sense. It should be pointed out here that this involved an improvement in the patient's condition rather than a cure.
[75] Menasche et al. 2001.
[76] Strauer et al. 2001.
[77] Koch 2001.

contribution to our understanding of the mechanisms on which proliferation and differentiation in embryonic development are based.

Scientists hope that more detailed examination of the processes of embryo development will provide information on the causes of infertility, abnormal embryonic development, spontaneous abortion and congenital anomalies. There is also speculation as to whether certain diseases, such as juvenile diabetes, might have their origins in early embryonic development.[78] This relates to information in the area of developmental biology, the benefits of which, in terms of new therapeutic approaches, are still to be discovered.

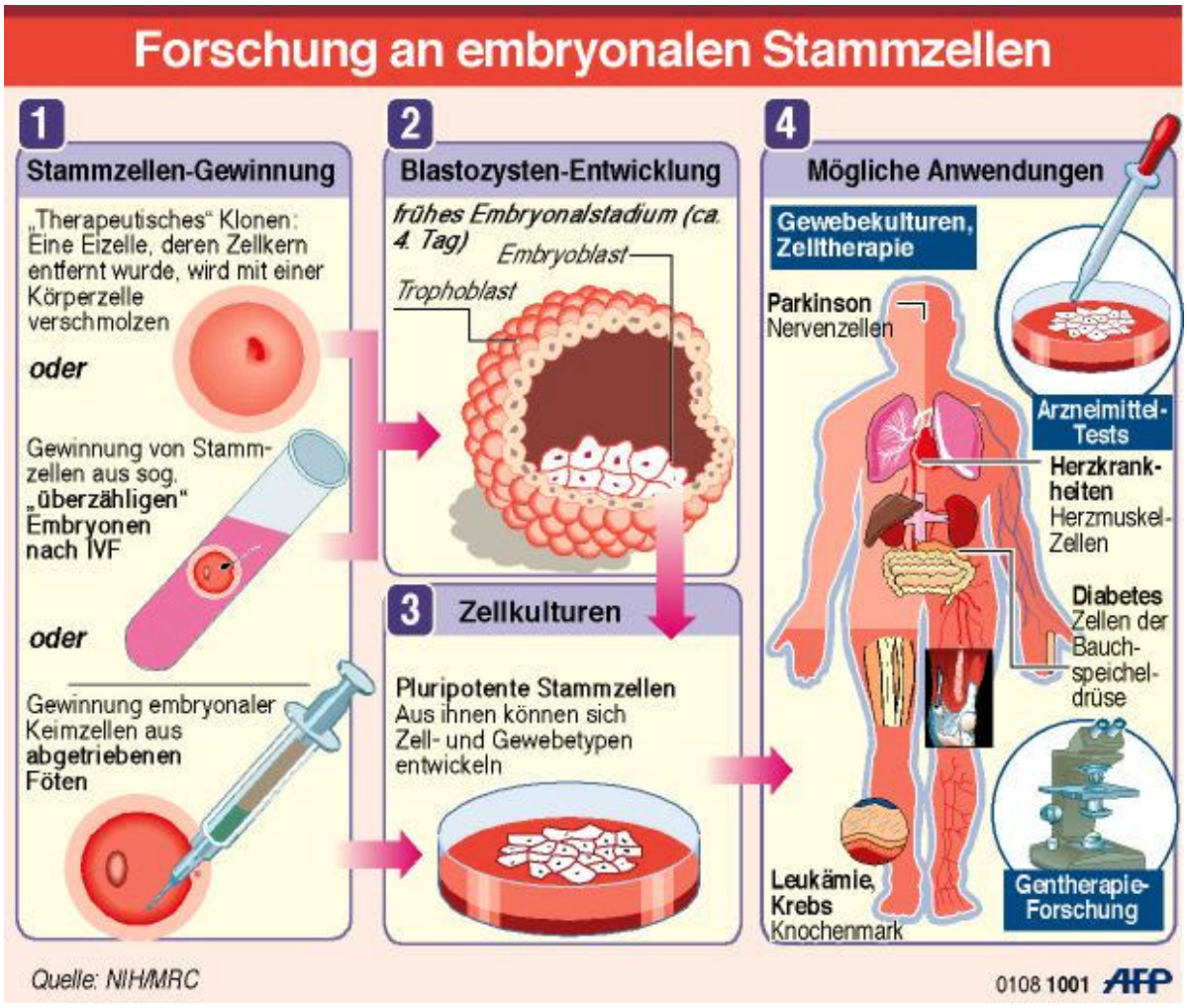

Figure 3

It is also hoped that research mainly in ES cells will lead to a better understanding of the development and regulation of early stem cell stages and of the mechanisms on which the

[78] National Bioethics Advisory Commission 1999, p. 17.

capabilities of self-regeneration, proliferation and differentiation rely. Opinions vary amongst researchers as to whether these investigations are a necessary prerequisite for obtaining information on the way in which the differentiation of adult stem cells can be steered in particular directions, with a view to their use in regenerative cell therapy. Whether information obtained from ES cell research is applicable to adult stem cells is also unclear.

Particular attention will need to be paid to the differences between embryonic and adult stem cells. Among the fundamental problems associated with the potential therapeutic use of ES cells are the necessary purity of cell types, the risk of tumour formation and the transfer of pathogens from the nutrient media, since these contain living animal cells. Information is also being sought concerning the mechanisms of transdifferentiation and reprogramming of cell nuclei from somatic cells following cell nuclear transfer.

With AS cells, the main priority is to overcome difficulties associated with the derivation and replication of cells and those related to the purity of cell types. Whether AS cells can be obtained in adequate quantity from elderly patients must also be clarified. The risk of malignancy in therapeutic use is presumably lower in view of the more limited ability to proliferate.

The extent to which findings from animal experiments are applicable to humans has not yet been clarified. A number of fundamental differences have been identified in the embryonic development of mice and humans and in investigations in ES cells it has been found that various substances have an effect on human cells which is completely different from that seen in mouse cells. Research in human ES cells is therefore expected to provide important insights into the specific characteristics of human embryonic development. Research in ES cells from non-human primates could contribute to our understanding of these peculiarities.

1.1.3.2 Cell and tissue replacement

In the context of what is known as regenerative medicine, stem cells could attain particular therapeutic importance with regard to those tissues which in adult humans exhibit only very little or no ability to regenerate. This applies in particular to the central nervous system. Possible areas of use for stem cells in cell and tissue replacement include not only neurodegenerative diseases such as Parkinson's disease and Huntington's chorea but also myocardial infarction, stroke, paralysis, epilepsy, diabetes mellitus (type I) the leukaemias and deficiencies of the immune system (cf. Appendix I).

The therapeutic use of stem cells beyond the present procedures in which adult stem cells are used for regeneration within their tissue specificity[79] will not be an option within the

[79] Cf.1.1.2 Application and use.

foreseeable future. Quite apart from the ethical problems, considerable technical and scientific difficulties are still to be overcome.

Problems with the use of stem cells for cell and tissue replacement lie mainly in the fact that the cells are difficult to culture and also that deliberate differentiation to a particular cell type is not yet possible. It is also unclear at present whether and to what extent integration and tissue-specific function of these cells can be achieved at all in the human body.

As far as is known to date, one particular stem cell type will probably not be sufficient for cell therapy in the various forms of disease listed above.[80] Systematic and comparative studies in particular into the proliferation and development potential of stem cells of various origins is therefore necessary, in order to determine their regenerative potential.

With respect to the use of stem cells in cell and tissue replacement, a distinction must be made from the clinical point of view between allogeneic (heterologous) and autologous cells. Whereas allogeneic cells have a genetic identity different from that of the individual receiving the tissue, in the case of autologous cells the genetic pattern is identical. ES cells and EG cells would belong to the allogeneic category. AS cells[81] and neonatal stem cells[82] might fall within both the allogeneic and autologous categories. ES cells produced by cell nuclear transfer would presumably behave as quasi-autologous cells.

Immunological rejection reactions are to be expected with the transplantation of allogeneic cells or tissues, as seen in organ transplantation. Accordingly, after the transplantation of these cultured cells, suppression of the immune response would be necessary and this is associated with a number of side effects. As with tissue typing in organ donation, it would be possible to classify donor cells in tissue banks according to histocompatibility categories. Unlike donor organs, however, it is also conceivable that the genetic characteristics of the cells could be modified before they were stimulated to differentiate. In this way particular genes whose products are involved in triggering rejection reactions could be switched off. However, no experience in this area is available to date.

After the transplantation of autologous cells, no immunosuppression would be required.[83]

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[80] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.

[81] The use of heterologous AS cells may be considered for the following reasons: autologous cells show a gene defect which was responsible for the original disease; shortage of time at the start of treatment; reprogramming procedure too expensive for individual application. Moreover, the triggering of a slight immunological defence reaction is actually desirable in the treatment of certain malignant diseases (graft-versus-leukaemia or graft-versus-tumour reaction).

[82] Stem cells from cord blood might have to be used because stem cells have been frozen to date only from a few new-born infants.

[83] The possibility has been discussed that even with ES cells from cell nuclear transfer ("therapeutic" cloning), "mild chemotherapy" might be necessary to inhibit the immune reaction caused by mitochondrial DNA from the egg cell.

1.1.3.2.1 Cell and tissue replacement from ES cells (allogeneic, heterologous method)

An investigation has shown that donor cells developed from ES cells were capable of forming new myelin sheaths in an animal model of a rare human myelin disorder, Pelizaeus-Merzbacher disease.[84] Similar strategies could possibly be used for the treatment of common myelin disorders such as multiple sclerosis. However, multiple sclerosis is an autoimmune disease and therefore in this respect not comparable with the hereditary Pelizaeus-Merzbacher disease. Moreover, animal experiments have been conducted in animals whose brains were still developing. Transfer of the findings to humans is questionable, particularly with regard to diseases in adulthood. Also, for diseases affecting large areas of the brain, such as Alzheimer's disease, successful cell transplantation is thought to be improbable, particularly since cell replacement therapy does not treat the causes of the disease (with Alzheimer's, the development of protein plaques, so that lasting success of treatment with stem cells (of whatever origin) appears unlikely.[85]

The first successes in animal experiments have been reported with differentiation into insulin-producing cells and dopaminergic neurones for the treatment of diabetes mellitus and Parkinson's disease and the replacement of heart tissue in certain forms of heart failure.[86] Long term studies concerning the further development and function of transplanted cells in the host animal have not yet been carried out. In particular with the transplantation of nerve cells and their precursors, problems must be expected that cannot be solved by the availability of stem cells alone. Patients with Parkinson's disease have been treated in various studies with cells from aborted fetuses[87]. One of the most recent studies found severe side effects in 15% of patients after transplantation, in particular severe disorders of movement or dyskinesias.[88] The clinical benefit was more limited than in previous studies and could be seen only in younger patients. The authors concluded from these findings that both the procedural technique and also the location of transplantation required further discussion. Such questions will also need to be clarified for the transplantation of stem cells.

The question of whether specific donor cells can also be derived from human ES cells in a similar way and the extent to which these can restore the function of defective organs or tissues after transplantation can only be answered by research in human ES cells. Initial indications could probably be obtained in experiments with ES cells from non-human primates, although even research in non-human primates is associated with scientific, ethical and economic problems.

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[84] Brüstle et al. 1999.
[85] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.
[86] Klug et al. 1996; Lee et al. 2000; Soria et al. 2000; Lumelsky et al. 2001.
[87] These were not the EG cells described earlier, but precursors of nerve cells that produce the messenger substance dopamine, present in abnormally low concentrations in patients with Parkinson's disease.
[88] Freed et al. 2001.

1.1.3.2.2 Cell and tissue replacement from cell nuclear transfer (autologous method)

No findings are yet available relating to the use in transplantation of ES cell lines produced by cell nuclear transfer. It is not yet known whether abnormal development of the cells and tissues produced can occur after "therapeutic" cloning which would exclude their use for transplant purposes in humans. When ES cells created by cell nuclear transfer are used, abnormal development can occur either during the differentiation process itself or later, during interaction with the surrounding tissues in the organism. In animal experiments on reproductive cloning a large number of developmental abnormalities were observed.[89]

1.1.3.2.3 Cell and tissue replacement from EG cells

No detailed investigation has yet been carried out into the regenerative potential of EG cells compared with ES cells. Nor can any prediction yet be made as to whether and to what extent the different imprinting status of ES cells compared with EG cells will affect the ability to differentiate and the long term behaviour in the organism of donor cells derived from EG cells.

1.1.3.2.4 Cell and tissue replacement from neonatal stem cells

No experience is yet available of the use of transdifferentiated neonatal stem cells. The use of mesenchymal stem cells from cord blood for the formation of bone and cartilage is planned in the USA.

Compared with AS cells, the possibilities of an undetected hereditary disease, infection acquired in the uterus or bacterial contamination occurring during delivery make the use of cord blood appear potentially more problematic than that of allogeneic, and particularly autologous adult stem cells.

1.1.3.2.5 Cell and tissue replacement from AS cells

Investigations in AS cells are currently at a considerably more advanced stage than research in ES cells.

The identification of factors affecting either the proliferation or differentiation of AS cells or leading to reprogramming after cell nuclear transfer, could be used to treat AS cells outside the body and then to transplant them back into the patient. The development of new types of active substances and medications is also conceivable, however, which may activate the regeneration of damaged tissue by means of replication and differentiation of tissue-specific stem cells directly within the organism.[90] Diseases due to a genetic defect could be treated either with allogeneic (heterologous) AS cells or with autologous cells subjected to gene

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[89] Cf. 1.1.1.2.1 Derivation.
[90] Verbal communication by PD Dr. Wobus at the closed hearing on 23 April 2001.

therapy prior to transfer. However, if the assumption that the number of somatic stem cells decreases with age proves correct, this may considerably limit the scope for using a patient's own stem cells for autologous cell replacement.

Animal experiments with AS cells have been limited largely to transplanting tissue-specific cells to a different environment. The many investigations carried out so far have therefore not shown whether transdifferentiated AS cells can also adopt the function of the tissue or whether they merely show its surface characteristics.

However, there are also studies in animals which indicate that cells arising from bone marrow stem cells can form new heart tissue with myocardial cells and blood vessels and improve cardiac function.[91]

From precursor cells in the pancreas of mice and humans, insulin-producing cells have been obtained that achieve temporary insulin independence in the mouse.[92]

Neural stem cells can lead to the formation of new myelin sheaths in mice with a certain myelin disease.[93] [94]

Investigations have not yet been carried out to determine whether the suitability of AS cells for therapeutic use is limited by the fact that stem cells have already accumulated DNA damage over their life span.

1.1.3.3 Organ replacement

The development from stem cells of complex organs such as the heart, kidney or liver is also discussed within the research community. Functional structures are to be formed by the combination of living cells and three-dimensional synthetic frameworks.[95] A major difficulty, however, is the need for an adequate blood supply to the organ and its connection to the nervous system. It is therefore assumed that the development of organs cannot be simulated in cell culture in the foreseeable future and that this must at present be regarded as rather unrealistic.[96]

1.1.3.4 Gene therapy

The availability of stem cells in vitro allows their use as carriers of genes which are intended to have therapeutical effect. Genetic changes in the cell prior to transplantation could overcome some of the difficulties associated with the strategies of gene therapy used to date, e.g. risks of

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[91] Kocher et al. 2001; Orlic et al. 2001.
[92] Bonner-Weir et al. 2000; Ramiya et al. 2001.
[93] This is a different myelin disease from that in the experiments of Brüstle et al. 1999.
[94] Yandava et al. 1999.
[95] Kaihara / Vacanti 1999.
[96] Verbal communication from Prof. Dr. Brüstle at the closed hearing on 23 April 2001.

viral infection and limited possibilities of control with regard to the location of integration of DNA. Only those cells found in vitro to have incorporated the therapeutic genes successfully would be transplanted.

Genetic modification of stem cells prior to differentiation could also switch off particular genes involved in the triggering of rejection reactions.

By contrast with ES and EG cells, information regarding the possible genetic modification of AS cells is currently patchy.[97]

1.1.3.5 Toxicity testing and the development of drugs

Human ES cells can be used to investigate the effects of drugs, chemical substances and environmental factors on embryonic development and differentiation processes in a cell model. Such embryotoxicological investigations have so far been carried out in experiments on animals or other cell cultures. The method has been tested successfully in mouse ES cells.[98] It is assumed that EG cells can be used for these methods in the same way as ES cells. However, the development stage of EG cell lines cannot be determined exactly since terminations of pregnancy can take place at different times.

The ability of stem cells to differentiate into various cell types further allows the pharmacological effects of active substances to be analysed in a broad spectrum of human cells.[99] The results of these studies allow conclusions to be drawn regarding the situation in humans to a much greater extent than those obtained previously in cell cultures of animal origin. It is probable that all stem cells, irrespective of their method of derivation, can be used for this type of investigation.

1.1.4 Medical and technical alternatives

With respect to cell and tissue replacement, alternatives to stem cell research can be tested only in relation to concrete therapeutic procedure and prevention strategies. In the treatment of juvenile diabetes, for example, there is the long-established method of insulin treatment which can be further improved by further development of the dosage forms. For myocardial infarction and various forms of heart failure, drugs are available that are undergoing continuous further development. The availability of stem cells for transplantation could represent progress in this area with the regeneration of cells and tissues. However, a cure may be difficult to achieve even with stem cells: if it were possible, for example, to normalise insulin production in the

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[97] Verbal communication from PD Dr. Wobus at the closed hearing on 23 April 2001.
[98] Spielmann et al. 1997; Scholz et al. 1999.
[99] The method offers particular advantages compared with the cell culture experiments currently used with regard to those cell types which are difficult to obtain from humans (e.g. neuronal cells) or those which cannot be maintained in culture for long periods and therefore require continuous harvesting.

pancreas in juvenile diabetics by means of stem cell therapy, the underlying immunological process directed against each insulin-producing cell would probably remain unchanged and would also damage the transplant.[100]

For many of the diseases for which stem cell therapy could be considered, there is at present no satisfactory treatment.

The possibilities of non-technical prevention (prevention of addiction, nutritional education etc.) as alternatives and the question of allocation of resources will not be discussed in this report, although this subject is of great importance.

With respect to the use of stem cells in gene therapy and the toxicity testing and development of drugs, alternative methods are already available, though the efficiency of these could be increased by the new methods.

For research into the underlying processes of human embryonic development at cell level, there appears to be no alternative to research in human embryonic stem cells. Insofar as this research in humans reaches boundaries which must not be crossed or is rejected for ethical reasons, there remains the possibility of obtaining general information by means of animal experimental research particularly in non-human primates (monkeys). The extent to which such information is applicable to humans remains uncertain.

1.2 Legal regulations (national/international)

1.2.1 Internationally valid regulations on research in embryos and human embryonic stem cells

1.2.1.1 UNESCO, United Nations and WHO

The "Declaration on the Human Genome and Human Rights"[101] passed by UNESCO on 11 November 1997 and ratified (endorsed) by the General Assembly of the United Nations on 9 December 1998, emphasises the need for human dignity to be respected in research in human embryos. Reproductive cloning is also judged to be a practice contrary to human dignity.

At the level of international law, this is a political declaration from which only a political obligation arises, although having a possible pioneering function in preparation for a legally binding agreement.

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[100] The underlying feature particularly of juvenile diabetes is the ongoing destruction of insulin-producing cells in the pancreas by immunological processes directed against these cells. Abolition of the resulting insulin deficiency, whether by injection of insulin or by stem cell therapy, would therefore not change the actual cause of the disease.

[101] UNESCO 1998.

The WHO resolution at the 51st World Health Assembly reached the same conclusions[102], while following and recognising potential major advantages for clinical treatment in the further development of techniques of non-reproductive cloning, which it acknowledged at the 52nd World Health Assembly[103].

Alongside this, the International Federation of Gynaecology and Obstetrics (FIGO) has published ethical guidelines[104] on topics including

- research in embryos prior to nidation (1989),
- handling of fetal tissue (1992),
- donation of genetic material for human reproductive purposes (1994),
- modification of the human genome (1996),
- sale of gametes and embryos (1996),
- patenting of human genes (1997),
- cloning (1998).

Although the guidelines do not deal explicitly with the use of stem cells, it is clear that the scientific use of embryonic tissues from embryos prior to the formation of the primitive streak or of post-mortem fetal tissue is regarded as permissible. Since the regulations described are much less restrictive than those of the German Embryo Protection Act and moreover the Medical Associations responsible for the development of professional regulation in Germany were not involved in the preparation of these guidelines, the FIGO guidelines have so far played no fundamental role in Germany.

The declarations, explanations and resolutions which have played a more important part in the development of professional ethics and therefore of professional regulation are those of the World Medical Association (WMA).[105] The German regional medical councils are represented within the World Medical Association by the German Medical Association. The World Medical Association has also issued no comment to date on research in embryonic stem cells. Here again, however, there are a number of documents that deal indirectly with the use of embryonic cells. The declaration on the transplantation of fetal tissue[106] prepared in 1989 preceded the German Medical Association's 1991 "Guidelines for the use of fetal cells and fetal tissues"[107] and the German Medical Association guidelines follow the basic statements of the World Medical Association declaration.

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[102] World Health Organisation (WHO) 1998.
[103] World Health Organisation (WHO) 1999.
[104] For original documents see International Federation of Gynecology and Obstetrics 2001.
[105] Weltärztebund (WMA) 2000.
[106] Contained in Weltärztebund (WMA) 2000.
[107] Bundesärztekammer (1991).

A declaration on "In-vitro fertilisation and embryo transfer"[108] in 1987, however, was rejected by the independent administrators of the German medical profession, due to its less restrictive attitude to surrogate motherhood and its lack of attention to the well-being of the child. This position was later also adopted by the German Bundestag in the Embryo Protection Act. Further attempts by individual national organisations to loosen the restrictions with regard to gamete transfer and surrogacy, after many years of discussion, obtained no majority within the World Medical Association.

In a declaration on "Donation and transplantation of organs and tissues"[109] in 2000, the World Medical Association recommended a moratorium on xenotransplantation, the transplantation of brain tissue and gonads and the use of cell nuclear replacement technologies ("therapeutic" cloning).

The 1964 "Recommendations for physicians engaged in biomedical research in humans", which have become known as the Declaration of Helsinki, set out requirements for the behaviour of physicians in human experimentation.[110] The Declaration has been incorporated in the main fundamental regulatory systems for doctors dealing with individuals taking part in trials, such as the draft professional regulations of the German Medical Associations, the German Medicines Act, the European Guidelines for Good Clinical Practice[111] and the CIOMS guidelines[112]. The Declaration of Helsinki describes in particular precautions for the protection of individuals taking part in trials, for example, the voluntary giving of informed consent, the activity of ethics committees and research transparency. The revised version of the Declaration of Helsinki in 2000 includes for the first time "research in identifiable human material or identifiable data". The use of human (embryonic) stem cells therefore also falls under the sphere of regulation of the Declaration of Helsinki.

1.2.1.2 Council of Europe

The “Convention for the protection of human rights and human dignity with regard to the application of biology and medicine – the Council of Europe Convention on human rights and biomedicine” dated 4 April 1997[113] sets minimum standards for national legislation for the limitation of medical interventions and research projects. The Convention has in the meantime come into force, in the states which ratified it[114], as an international undertaking for

[108] Contained in Weltärztebund (WMA) 2000.
[109] Contained in Weltärztebund (WMA) 2000.
[110] Weltärztebund (WMA) 1964.
[111] Europäisches Parlament 2000.
[112] World Health Organisation 2000.
[113] Europarat 1997.
[114] The Convention has been signed by 30 States to date; of these, 10 have already ratified it (Czech Republic, Denmark, Georgia, Greece, Portugal, Rumania, San Marino, Slovakia, Slovenia, Spain). - Status: 10 October 2001 (Europarat 2001).

intranational implementation. Following controversial discussions in the public domain, the Federal Republic of Germany has not yet taken a decision regarding signature and ratification of the Convention.

According to Article 18 (1) of the Convention, it is at the discretion of the individual States whether they allow embryonic research or not. Those who allow research on embryos must guarantee "appropriate protection" of the embryo in their legal regulations. The creation of human embryos for research purposes is prohibited (article 18 (2)). According to article 27, States who are signatories to the Convention are permitted to set up national regulations over and above the standard of protection provided by the Convention. According to article 36, these States are also permitted to retain regulations deviating from the Convention if they declare the corresponding reservation on signing or ratifying the Convention.[115]

According to Art. 31, for further elaboration of the principles of the Convention, additional protocols can be prepared, the signing and ratification of which can take place, however, only after signature and ratification of the Convention. At present, additional protocols have been prepared on medical research and on protection of the embryo. An additional protocol concerning the ban on cloning of human life was agreed on 12 January 1998 by the ministerial committee of the Council of Europe.[116] According to Art. 1, any intervention with the intention of creating a human individual that is genetically identical to another living or dead human individual is prohibited. Genetic identity is defined in Art. 1 as existing where a common nuclear genome is present. Art. 2 - contrary to the terms of the Convention - prohibits any deviation from the provisions of the additional protocol. Art. 3 states that the additional protocol is to be regarded as a supplementary article to the Convention.

1.2.1.3 European Union

According to Art. 6 (1) of Regulation 98/44/EG of the European Parliament and the Council concerning the legal protection of biotechnological inventions dated 6 July 1998[117], known as the EU biopatent guideline, the inventions whose commercial exploitation would contravene public order or good moral practice cannot be patented. In this context, the following in

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[115] This is significant, e.g. for the licensing of "therapeutic" cloning in Great Britain, which is prohibited by Art. 18 (2) of the Convention (Production of embryos for research purposes). In addition to the contractual reservation, the instrument known as the Declaration of interpretation should also be mentioned here. While contractual reservations are subject to the rules of the Vienna Convention on the law of contracts (Art. 19-23) and the more specific rules of the contractual system concerned (in this case Art. 36), declarations of interpretation offer further latitude for signatories (see Art. 31 of the Vienna Convention on the law of contracts). In the present case, particular mention should be made of the Declaration of interpretation made by the Netherlands in relation to the supplementary protocol on cloning dated 4 May 1998. This establishes that the Netherlands understands "human being" to mean only "human individual, i.e. a human being who has been born".

[116] Europarat 1998.

[117] Europäisches Parlament und Rat 1998.

particular are not patentable (Art. 6 (2)): procedures for the cloning of human individuals, procedures for the modification of genetic identity of the germ line of human individuals and the use of human embryos for industrial or commercial purposes.

The "European Group for Ethics in the Sciences and the New Technologies at the European Commission", in its statement of 14 November 2000, called for strict public controls by a centralised body for those countries in which research with embryonic stem cells is permitted. It also called for guarantees that, in both private and public institutions, approval could be given for such research work only in individual cases and ensuring the maximum possible transparency.

1.2.2 Overview of legal regulations in selected states

A comparative examination of European law reveals that the German Embryo Protection Act sets a very high level of protection for the embryo in vitro by comparison with other European and international standards. With regard to the great diversity of legal regulations pertaining in the European states, these can be divided roughly into three levels of protection:[118]

A number of states completely prohibit embryo research or allow it only for the maintenance of the actual embryo concerned. Apart from Germany, these include Ireland, Luxembourg, Austria, Switzerland, Norway and Italy. Other states, although they allow research which need not benefit the embryo itself, insist on a research objective that provides a “group benefit” in the broader sense, i.e. the research must for example relate to the improvement of techniques for assisted fertilisation or the avoidance of miscarriage. These are Denmark, France and Sweden. Other states permit even wider research. The possibilities here are limited merely by the fact that such research is permitted only within the two weeks following fertilisation. These are Finland, Greece, Great Britain, the Netherlands and Spain.

Otherwise, the regulatory structures internationally vary enormously, from “regulation” by committee decisions and guidelines to differentiated legal provisions for embryo research. Appendix II lists the regulations of a handful of states, by way of example, no attempt at a uniform basis of comparison being possible in view of the diverse levels of information available on the individual states.

[118] According to a list drawn up by the Bioethics Research Office at the University of Münster.

1.2.3 Legal regulations relating to stem cell research in the Federal Republic of Germany

1.2.3.1 Embryo Protection Act (Embryonenschutzgesetz, ESchG)

The legal aspects of research in embryos and the harvesting of stem cells from embryos are regulated by the Embryo Protection Act (ESchG).

The Embryo Protection Act of 13 December 1990, which came into force on 1 January 1991, is an Act to prevent the misuse of artificial fertilisation and of the human embryo in vitro (§§ 1 to 4) and of certain techniques such as germ line modification, cloning and the formation of chimeras and hybrids ((§§ 5 to 7). This is based purely in criminal law and therefore represents only a partial system of regulation of the medical application of artificial fertilisation technology. Only in 1994 was overall legislative competence in "artificial fertilisation in humans, the investigation and artificial modification of genetic information and regulations concerning the transplantation of organs and tissues" transferred to the Federal government (Art. 74, (1) no. 26 of German Basic Law (Grundgesetz, GG)).

The Embryo Protection Act is founded on the principle that embryos in vitro are wholly worthy of protection. The legal regulation covers the embryo in vitro up to its nidation in the uterus of a woman. Nothing must be done to the embryo that is not for its own maintenance.[119] The artificial fertilisation of an egg cell and hence the creation of an embryo in vitro is permitted only for purposes of giving rise to a pregnancy.[120]

An embryo as defined in the Embryo Protection Act is "the single fertilised human egg cell capable of development, from the time of nuclear fusion onwards, and further any totipotent cell derived from an embryo which is capable, given the further necessary conditions, of dividing and developing into an individual."[121]

The creation of embryos for research purposes and research in embryos and individual totipotent cells is therefore prohibited. The prohibition extends to such embryos produced for the purpose of bringing about a pregnancy, but which can not longer be used for that purpose, perhaps because of non-temporary illness of the woman. With the stipulation that no more egg cells may be fertilised than can be transferred to the woman within one cycle and that no more

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[119] § 2 (1) ESchG: "Any person disposing of a human embryo created outside the body or taken from a woman before completion of its nidation in the uterus or giving away, acquiring or using it for purposes other than its maintenance will be liable to imprisonment for up to three years or a monetary fine." (2): "Any person undertaking the further development of a human embryo outside the body for a purpose other than to give rise to a pregnancy will also be liable to punishment."

[120] § 2 (1) no. 1 ESchG: Any person undertaking the artificial fertilisation of an egg cell for a purpose other than to lead to the pregnancy of the woman from whom the egg cell originates,……. will be liable to imprisonment for up to three years or a monetary fine."

[121] Cf. § 8 (1) ESchG.

than three embryos may be transferred within one cycle (§ 1 (1) nos. 3 and 5), the Embryo Protection Act aims to avoid the creation of “supernumerary” embryos, that is, embryos that are permanently incapable of being used to bring about a pregnancy.[122]

In the report, these embryos that can no longer be used to bring about a pregnancy are described as “supernumerary embryos”. In public discussion, for various reasons, the terms “orphan embryos” or “embryos with no prospect of life” are used synonymously.

Also prohibited is the harvesting (removal) of stem cells from embryos, whether or not these cells are totipotent or pluripotent and whether or not the embryo is thereby destroyed.[123]

Research in pluripotent embryonic stem cells is not, however, prohibited under the Embryo Protection Act. These are no longer capable of developing into an individual[124] and are therefore not included within the scope of protection of the Embryo Protection Act. The intention of the Embryo Protection Act was to limit the criminal ban deliberately to the protection of particularly high-priority objects of protection under the law, taking account of the value judgement made by the Constitution in favour of human dignity and life.[125] Efforts to produce a viable embryo by the reprogramming of pluripotent cell material contravene the law just as much as research in these embryos.

The removal of a totipotent cell, as it constitutes cloning, is also prohibited. The act of cloning is defined as: "any person artificially causing a human embryo to be created with the same genetic information as another embryo, fetus, human or cadaver ..."[126]. The removal from an embryo of a totipotent cell (which is equivalent to an embryo) gives rise, in fact and in law, to two embryos (embryo splitting).

Apart from reproductive cloning, a further method for the derivation of embryonic stem cells known as "therapeutic cloning" also contravenes the ban on cloning. In this case the embryo is

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[122] The Embryo Protection Act has achieved the intended effect in that, after being in force for ten years, to the knowledge of the authorities there are few such “supernumerary” embryos. On this subject and on the problem of pronuclei, cf. 3.1.1 Derivation of ES cell lines.

[123] Stem cells are derived from the inner cell mass of the blastocyst of an approx. four-day-old embryo. According to current knowledge, the embryo is destroyed by this process, cf. Deutsche Forschungsgemeinschaft 2001b, p.13.

[124] Cf. 1.1.1.6 Totipotency/Pluripotency: According to current scientific and technical knowledge, the cells taken from the blastocyst for the harvesting of stem cells are dependent on the blastocyst cell group for their ability to develop into an individual. No individual can develop from isolated cells outside this blastocyst cell group. However, doubts have occasionally been cast on this assumption. Cf. 1.1.1.6 Totipotency/Pluripotency.

[125] Cf. draft federal government legislation: Draft of a law for the protection of embryos (Embryo Protection Act - ESchG), BT Printed paper 11/5460, p.6. The explanatory notes to the Act read: "The draft limits itself deliberately to criminal prohibition only where this appears necessary for the protection of particularly high-priority objects of legal protection. In particular, it takes account of the value judgements of the Constitution in favour of human dignity and life ..."

[126] § 6 (1) ESchG: "Any person artificially causing a human embryo with the same genetic information as another embryo, fetus, human or cadaver to be created will be punished by imprisonment for up to five years or with a fine."

created by transfer of the cell nucleus of a somatic cell (body cell) into an enucleated egg cell. This, like a naturally fertilised egg cell, can develop in culture to a blastocyst, from which stem cells can then be harvested that carry genetic information identical to that of the individual from which the somatic cell originated. It is suspected that therapeutic use of these stem cells or of tissue obtained from them would trigger no immunological reaction in the individual from which the genetic information (cell nucleus) originated.[127]

The result of this method, in the terms of the Embryo Protection Act, would be that a human embryo was created. It is true that the definitions of § 8 ESchG assumes the creation of an embryo by means of fusion of the cell nuclei of egg and sperm cells (each with their haploid sets of chromosomes). No such fertilisation takes place when a cell nucleus is transferred into an enucleated egg cell, since the transferred cell nucleus has a complete (diploid) set of chromosomes. The word "already" in § 8 (1) ESchG, however, makes is sufficiently clear that the provision, according to the intention of the law, to provide comprehensive protection for the human embryo, contains no conclusive definition of terms. The intention is rather to ensure that legal protection begins from the early phase of development described, without excluding other forms of developing human life from this protection. The fact that the provision also includes the creation of an embryo by means of the cell nuclear transfer technique also makes it clear that not only embryo splitting but also the creation of an embryo with the same genetic characteristics as a fetus, human or cadaver, is covered by the prohibition. This form of cloning is only conceivable if the method of nuclear transplantation is used. An embryo in the sense of the Embryo Protection Act can therefore also be created in other ways, including cell nuclear transfer. The Federal Government also came to this conclusion in its Report on Cloning dated 26 August 1998.[128]

Embryos created by means of "therapeutic" cloning have the same genetic information as another individual under the terms of § 6 (1) ESchG. It is true that the method of cell nuclear transfer, in view of the genetic material contained in the cytoplasm of the enucleated egg cell, cannot in principle lead to the creation of a living individual whose genetic information is 100% identical with that of the individual from which the transferred cell nucleus was derived.[129] In humans, the cell plasma of the egg cell contains 13 protein-coding genes of mitochondrial DNA, though these represent, at 0.01 to 0.02%, only a minute proportion of the total human genome. The ban on cloning in § 6 ESchG, however, bases its prohibition on a legal and not a scientific definition of equivalence. The purpose of the standard is to place a comprehensive

[127] Deutsche Forschungsgemeinschaft 2001b, p.13.
[128] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and the further developments emerging (Report on Cloning), BT Printed paper 13/11263, section C, sub-section 1.2.2.
[129] Unless the somatic (body) cell and enucleated egg cell originate from the same female individual.

ban on the creation of copies of human individuals. The marginal DNA of the mitochondrial genes alone is insufficient to cast doubt on the concept of identical genetic make-up.[130]

Whether the provisions of §§ 6 and 8 ESchG in relation to "therapeutic" cloning satisfy the requirement for certainty of Art. 103 (2) GG (basic law) is highly questionable.[131] In order to remove uncertainties and to exclude possible loopholes with regard to statutory offences, in the “Klonbericht” (Report on cloning) dated 26 August 1998 the Federal Government gave notice of a legal clarification and proposed, amongst other things, to broaden the Embryo Protection Act by adding an offence which it prohibited in general, that is, the creation of an embryo by an asexual means, in other words, without the fertilisation of a human egg cell by a human sperm cell.[132]

The need for clarification of the legal situation was clear, however, in particular for the following reason:

It is conceivable that a researcher would not stop at the transfer of a somatic (body) cell into an enucleated egg cell, but might change the genetic information of the somatic cell nucleus by genetic manipulation prior to transfer into the enucleated egg cell. If this meant, even taking into account the above comments, that this could no longer be regarded as the creation of an embryo with the same genetic information, punishment for cloning under § 6 (1) ESchG would be ruled out. In this case, however, there would also be no contravention of the ban on artificial modification of the germ line in accordance with § 5 (1) ESchG[133], since somatic cells (body cells) are not germ line cells under the terms of § 8 (3) ESchG[134]. Even if one assumes that in the above case the genetic information of the cell nucleus of a germ line cell in the sense of § 8 (3) was manipulated, a contravention against the cloning ban fails since neither the modified cell nucleus nor the enucleated egg cell were used for fertilisation (§ 5 (4) no. 1[135], § 5 (2) ESchG[136]). Using this combination method, any number of human embryos could be produced, even with the use of somatic cell nuclei possibly from cadavers, without punishment.

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[130] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and the further developments emerging (Report on Cloning), BT Printed paper 13/11263, section C, sub-section 1.2.1.

[131] Höfling 2001a, p. 212 f.. Art. 103 (2) GG states: "An act can only be punished if the criminal nature of the act was determined in law before the act was committed."

[132] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and the further developments emerging (Report on Cloning), BT Printed paper 13/11263, section D.

[133] § 5 (1) ESchG: "Any person artificially modifying the genetic information of a human germ line cell will be liable to imprisonment for up to five years or punishment in the form of a fine."

[134] § 8 (3): "Germ line cells in the context of this Act are all cells in a cell line from the fertilised egg cell down to the egg and sperm cells of the individual created from it, and also the egg cell from insertion or penetration of the sperm cell to the point of fertilisation completed with fusion of the nuclei."

[135] § 5 (4) no. 1 ESchG reads: "Paragraph 1 does not apply to an artificial modification of the genetic information of a germ cell located outside the body, if the use of this cell for fertilisation is excluded."

[136] § 5 (2) reads: "Any person using a human germ cell with artificially modified genetic information for the purposes of fertilisation is also liable to punishment."

In the view of the "Report on cloning" dated 26 August 1998[137], this represents a serious loophole in the legislation which must be closed.

It is also dubious to what extent "therapeutic" cloning using an animal egg cell, that is, transfer of a human somatic cell (body cell) into an enucleated animal egg cell, as reported in the press[138], represents a contravention of the cloning prohibition under § 6 ESchG. The cloning ban is contravened if a "human embryo" is created. The viable human egg cell in itself constitutes an embryo under the terms of § 8 (1) ESchG (see above). If an animal egg cell envelope is used, this cannot be called a human egg cell, even if this is associated with a human cell nucleus.[139] The use of animal cell material was regulated by the legislator in § 7 ESchG (formation of chimeras and hybrids)[140], but the applicability of this here is dubious, since at least one human embryo is not being used and no fertilisation using an egg and sperm cell is taking place.

The Federal Government also saw the need to act here and proposed in the "Report on cloning" dated 26 August 1998 to design the regulation of § 7 so that the technique of nuclear transplantation using animal material is clearly covered by the provisions of § 7.[141]

1.2.3.2 Validity of the Embryo Protection Act

The area of validity of the Embryo Protection Act is determined by the Criminal Code.[142] The reference point for prosecution is the territorial principle (§ 3 Criminal Code (StGB)[143]), which relates to the place of the act and not to the individual committing the act. Only contraventions committed in Germany are punishable, though this includes criminal participation (instigation and assistance) in an act punishable under German criminal law committed in another country, where the individual concerned acted within Germany.

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[137] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and the further developments emerging (Report on Cloning), BT Printed paper 13/11263, sub-section 3.1 and section D.

[138] "China finances cross between human and animal cells" 2001. There have also been press reports concerning patent applications involving this technology, e.g. by Stem Cell Sciences, Australia and Biotransplant, USA.

[139] Keller / Günther / Kaiser (1992) § 6 note 5.

[140] § 7 reads: "(1) Any person undertaking, 1. to combine into a group of cells embryos with different genetic information using at least one human embryo, 2. to combine with a human embryo a cell containing different genetic information to that of the cell and capable of differentiating further with this, or 3. to create an embryo capable of differentiation by fertilising a human egg cell with the sperm of an animal or by fertilising an animal egg cell with the sperm of a human, will be liable to imprisonment for up to five years or a fine. (2) Any person undertaking, 1. to transfer an embryo created by a procedure as in (1) to a) a woman or b) an animal or 2. to transfer a human embryo to an animal, will also be liable to punishment."

[141] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and the further developments emerging (Report on Cloning), BT Printed paper 13/11263, sub-section 8.2 and section D.

[142] The following comments are excerpts: Wolfrum 2001.

[143] § 3 StGB reads: "German criminal law applies to acts carried out within Germany."

The import of embryos and of the totipotent cells equivalent to these is punishable under § 2 (1) ESchG[144], which forbids the distribution and the acquisition of an embryo (within Germany). The method by which the embryo or totipotent cell was created in the other country is of no significance here.

The importation, distribution and acquisition of pluripotent embryonic stem cells is not prohibited, since these are not equivalent to embryos under the terms of the Embryo Protection Act.[145] However, this presupposes that the persons importing the embryonic stem cells are not to be regarded under criminal law as instigators or assistants within Germany of those who produced the embryonic stem cells abroad, e.g. by their financial, technical or personal support or by ordering the imported stem cells to be produced. There must be no connection between the placing of an order for embryonic stem cells and their production. For the exemption from penalty which therefore exists for importation, the method of derivation of the embryonic stem cells abroad is not decisive, whether it was by the creation of what are known as research embryos, by "therapeutic" cloning or by the use of "supernumerary" embryos.

The derivation of human embryonic stem cells from primordial germ cells, isolated as precursor cells of egg and sperm cells from embryos or fetuses dying prematurely and developed in culture to EG cells[146], are subject to no legal regulation. The Embryo Protection Act does not apply, since it covers only the period up to nidation of the embryo in the uterus.

1.2.3.3 Other legal regulations for stem cell research

1.2.3.3.1 Transplantation Act (Transplantation Act and Medicines Act)

The Transplantation Act (Transplantationsgesetz) dated 5 November 1997 excludes blood, bone marrow and also embryonic and fetal tissues and organs from the sphere of application of the Act. In so far as embryonic and adult stem cells are used for the purposes of treatment or medical research in the patient, the Medicines Act (Arzneimittelgesetz) applies. For stem cell research not involving clinical use, this has no relevance.

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[144] Cf. footnote 119.

[145] According to the current state of scientific knowledge, it is assumed that human ES cells are pluripotent. Since human ES cells, unlike mouse ES cells which are clearly pluripotent, can also differentiate into trophoblast cells (Thomson 1998), in theory using the methods of Nagy et al. 1993 a viable embryo could be created in vitro from a human ES cell. Whether this is actually possible cannot be readily investigated for ethical reasons. However, should scientific research support the evidence that ES cells could become totipotent, under the current legal situation ES cells would have to be treated as embryos.

[146] Cf. 1.1.1.3 Embryonic germ cells (EG cells).

1.2.3.3.2 Transfusion Act

The Transfusion Act (Transfusionsgesetz (TFG)) sets the basic framework for the selection of donors, the technical and personnel requirements for the collection, storage and use of blood and the constituents of blood. The Transfusion Act does not regulate the derivation and use of stem cells, though it refers to guidelines for the collection of blood and constituents of blood and for the use of blood products (haemotherapy)[147,] which are to be drawn up by the German Medical Association in consultation with the Paul Ehrlich Institute, and in § 12 (1) no. 8 to the corresponding guidelines for blood stem cells.[148]

1.2.3.3.3 German Medical Association guidelines

As with the development of technical methods, "Guidelines for allogeneic bone marrow transplantation with unrelated donors" were first developed by the German Medical Association (1994).[149] These set down rules for the harvesting, processing and use of blood stem cells from bone marrow. While the "Guidelines for the transplantation of peripheral blood stem cells (1.6. 1997)"[150] were published in the preamble to the Transplantation Act by the Scientific Advisory Committee of the German Medical Association, in fulfilment of the legal order "Guidelines for the transplantation of stem cells from cord blood (14.5.1999)"[151] were prepared by the German Medical Association and the Paul Ehrlich Institute and general "Guidelines for the collection of blood and constituents of blood and for the use of blood products (27.7.2000)"[152] by the German Medical Association.

With respect to the Embryo Protection Act, no guidelines have so far been laid down for the derivation and use of embryonic stem cells.

The possible conflict between termination of pregnancy and research was regulated in the "Guidelines for the use of fetal cells and fetal tissues" prepared independently of an explicit legal order, by the German Medical Association.[153] Termination of pregnancy for the supposedly good purpose of research is prohibited, with other prohibitions including the payment of remuneration, the donation of fetal tissue for the benefit of specified recipients and the obtaining of maternal consent before the mother has taken the decision to terminate the pregnancy. The doctors harvesting and using the tissue are also required to be independent, and the interests of the mother are to be given priority in any conflict. The guidelines were prepared in particular in the context of the experimental use of fetal tissues or fetal cells in

[147] Bundesärztekammer 2000.
[148] Bundesärztekammer (Wissenschaftlicher Beirat) 1997.
[149] Bundesärztekammer (Wissenschaftlicher Beirat) 1994.
[150] Bundesärztekammer (Wissenschaftlicher Beirat) 1997.
[151] Bundesärztekammer and Paul Ehrlich Institute 1999.
[152] Bundesärztekammer 2000.
[153] Bundesärztekammer 1991. Under 2.3, 2.4, 2.5 of these guidelines.

transplant medicine. The guidelines bear no direct relation to the use of primordial germ cells (EG cells) for stem cell derivation, but are also relevant to this, since production of primordial germ cells requires the use of embryonic or fetal tissue.

2 The general ethical and legal problems of stem cell research

In the past, ethical problems surrounding research in embryos have often been the subject of discussion within the scientific and political community but also in the public arena. At the political level a number of commissions have already dealt with this topic in depth, for example the Study Commission on the Opportunities and Risks of Gene Technology, whose final report was published in 1987[154], or the Benda Commission, the name given to the joint working group of the Federal Minister for Research and Technology and the Federal Minister for Justice into in-vitro fertilisation, genome analysis and gene therapy.[155] Debates in the Bundestag on the Embryo Protection Act and regulation of the termination of pregnancy touched directly and indirectly on this area. The German Bundestag has taken a determined look at these problems at a number of sessions within this legislative period.[156] The German Research Association (Deutsche Forschungsgemeinschaft) attracted particular attention by publication of its position paper on stem cell research.[157]

At European level, a statement was recently made by the European Group on Ethics in Science and the New Technologies to the European Commission.[158] The European Parliament also adopted a resolution on the subject of human cloning.[159] In addition, the "Temporary Committee for Human Genetics and Other New Technologies in Modern Medicine" is also working at the European Parliament, and will present its final report in November 2001. The European Science Foundation has also published a position paper on stem cell research.[160]

There are also a large number of institutions in other countries, specifically addressing this topic. Major focal points have been, for example, the reports published by the British Committee of Enquiry into Human Fertilisation and Embryology, known as the Warnock Committee[161], the American National Bioethics Advisory Commission[162] and the NIH[163].

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[154] Bericht der Enquete-Kommission “Chancen und Risiken der Gentechnologie” 1987.
[155] Bundesministerium für Forschung und Technologie und Bundesministerium der Justiz 1985.
[156] Deutscher Bundestag 2001a and 2001b. Cf. also: Federal Government response to the major interpellation from Members, Ulrich Heinrich, Ulrike Flach, Cornelia Pieper, other Members and the Parliamentary FDP: The need for a broad public debate on "Therapeutic Cloning", BT Printed paper 14/6229.
[157] Deutsche Forschungsgemeinschaft 2001a.
[158] European Group 2000.
[159] In 1993 on the cloning of human embryos, in 2000 on the cloning of humans.
[160] European Science Foundation 2001.
[161] Committee of Inquiry into Human Fertilisation and Embryology 1984.
[162] National Bioethics Advisory Commission 1999.
[163] National Institutes of Health 2001a.

2.1 Worthiness of protection of the embryo

Before discussing the legal status of the embryo in vitro under the constitution, the ethical process of evaluation of this problem must be described.

2.1.1 Ethical evaluation

In the ethical assessment of new research technology, such as that currently developing in the area of human stem cell research, it is desirable to follow an assessment procedure which differentiates between means and objectives, initially questioning the legitimacy of the objectives which the research under consideration and the potential technology are supposed to serve. Since even high priority aims cannot justify every means, questions should also be asked concerning the acceptability of the means used, including any unintentional side effects and long term consequences. It is necessary to consider the social conditions that form the context for the objectives concerned and also to examine the social consequences to which the selected combination of objectives and means may lead.

2.1.2 The objectives of research in human stem cells

After a phase of research that related to tissue-specific (adult) human stem cells and tissue-specific and embryonic stem cells of animal origin, stem cell research entered a more intensive phase from November 1998. It was then for the first time that identification and derivation of pluripotent human stem cells began from "supernumerary" embryos (ES cells)[164] and from primordial germ cells from aborted embryos or fetuses (EG cells). This new phase involves both tissue-specific adult and also embryonic stem cells, the emphasis so far in the latter area – in accordance with the state of development of research – having been in the field of animal experimental research.

With regard to objectives, a distinction must be made between those towards which current research has mainly been directed and those for which the results of such research can be used beyond the intended sphere of application.

When considering the objective mentioned, it is appropriate to base their ethical evaluation on the ethical standards also expressed in the norms of fundamental constitutional law. These include as a priority the inviolability of human dignity, the right to life and to protection of the integrity of life and limb, rights of self-determination and personal rights and also the prohibition of discrimination. The norms established in criminal law, occupational law and in research ethics, particularly the ethics of research in humans, must also be observed.

[164] Cf. footnote 145.

In the light of these criteria, a distinction must be drawn between objectives to which a particular priority is attached and other objectives which must be regarded as ethically questionable.

2.1.2.1 Priority objectives of stem cell research.

2.1.2.1.1 Basic research and applied research

As is clear from the report on the current status of research, a large number of studies throughout the world are currently pursuing objectives in two areas, based on a variety of interests and evaluations:

- One of the purposes of research is to obtain information on the circumstances of biological development, which in humans are not yet fully understood. In particular, an understanding is required of the circumstances that lead to the differentiation of embryonic cells into the various tissue-specific cell types and of the factors that cause a somatic cell nucleus to redifferentiate after implantation into an enucleated egg cell. This is research of a basic nature, without which the development of appropriate treatments is impossible.
- There is also research that may be characterised as applied research, in that, in addition to obtaining information it also serves medical objectives. This includes in particular the development of treatments relating to diseases which medicine has so far been unable to address adequately and in which the use of tissue transplantation promises improvements in treatment. These include in particular the neurodegenerative diseases, diabetes mellitus, degenerative heart disease, etc.

In differentiating between basic and applied research, it must be borne in mind that that borderline between these two forms within modern research is fluid and in many areas difficult to identify. This is not least the case in view of research sponsorship, where the benefit of application often represents one of the prerequisites for sponsorship. The difficulty of distinguishing between the two forms of research also applies in the area of stem cell research.

It should also be mentioned that research, by its very nature, involves the risk of failure and that therefore any research – depending on its level of advancement – is subject to some degree of uncertainty as to whether, and within what period, the intended objective can be reached. This is particularly true of research in the biological sciences. As is clear from the current status report, stem cell research currently has some way to go to reach its targets, both in relation to establishment of the fundamental principles and also to the possible applications.[165] In individual limited areas (such as the use of haematopoietic stem cells in connection with the treatment of leukaemias) research has already succeeded in crossing the borderline into application. For most of the other high priority targets mentioned for discovery and action,

[165] Cf. 1.1.2 Application and implementation and 1.1.3 Expected future development.

however, it must be assumed that their realisation, where generally achievable, will require longer periods of research possibly of between 10 and 60 years.

Animal experimental research plays a particular role here, if the successful performance of animal experiments by conventional methods – initially in the form of studies in small animals, later in primates – is the prerequisite for the transition to studies in humans. Unusually, modern molecular biological research tends to investigate applicability to humans at an early stage, and then to proceed with animal experimental research.

In this context, as research stands at present, the fundamental knowledge required for the planned derivation of stem cells by reprogramming somatic cells is largely still lacking, and the preliminary animal experimental work required for the therapeutic use of embryonic human stem cells has not yet been completed. The applicability to humans of information obtained in the animal model has not yet been sufficiently established. For objectives such as the growing of organs from stem cells or the understanding of Alzheimer's disease, the principles are still so poorly understood that doubts persist regarding their general achievability.

In view of the status of this research, it is understandable that comparative statements regarding the opportunities and limits of various methods within stem cell research can be made, if at all, only with major reservations.

2.1.2.2 Assessment of these objectives

If the ethical criteria mentioned above[166] are taken as a basis, the objectives of obtaining knowledge and also of healing, alleviating and preventing disease are without doubt of particularly high ethical priority.

The priority to be attributed to the obtaining of knowledge by means of research is clear from the fact that according to Basic Law the freedom of research can be subject to no legal restriction, but only limitations inherent in the constitution (to be deduced from other basic rights).

The high priority of objectives pursued by applied research with a view to use in diagnosis, treatment and prevention, depends on the value attributed to the potential cure, alleviation and prevention of diseases in the context of health care. This is expressed in the constitutional regulations for the protection of the integrity of life and limb and the principle of the welfare state. It should be borne in mind here, that there are some objectives which may be regarded as achievable in the near future and others whose achievability cannot be determined without further research.

[166] Cf. 2.1.2 The objectives of research in human stem cells.

When pleading objectives of medical cure and prevention, it must be remembered that the very priority of these objectives can be used to associate with this plea other objectives that are ethically of lower priority or even questionable in themselves, not to mention the possibility that such a plea may be used to justify criminal experiments in humans, such as those which occurred during the period of national socialism. The objectives of treatment-related research can therefore only be regarded as high priority if they are desired by the patient and involve treatment for which the researcher is answerable in accordance with the rules of medical ethics.

In more detailed evaluation of such objectives, an important aspect is the level of urgency attributable to them from the point of view of health care and medical ethics. This depends not only on the degree of feasibility of the objective as mentioned above, but also on criteria such as the severity of the disease concerned, the number of individuals affected by it, the existence of alternative treatments, the degree of therapeutic success achievable and the resources to be invested.

Where research objectives have to be balanced against competing objectives or claims, the reasonable principle of research experimentation, that various promising paths to a research goal should be followed simultaneously, is subject to a limitation in the sense that the ethically and legally uncomplicated paths should be followed first, before investigating the feasibility of a method subject to competing ethical and legal claims. This means that ethically disputed research regarded as having high priority objectives cannot be given attention while ethically less controversial methods of research are being shown initial preference.

2.1.2.3 Unjustifiable objectives of stem cell research: reproductive cloning and germ line intervention

In addition to the stated aims of researchers - to gain information, to develop and improve the treatment of serious diseases - stem cell research can also be used for other objectives of questionable legitimacy, including objectives for which a therapeutic nature can be claimed as well as objectives outside the therapeutic spectrum. Amongst these are the use of the technologies developed by stem cell research in order to modify the germ cells that affect all progeny (germ line intervention), and in order to transfer a somatic cell nucleus into an enucleated egg cell to give birth to a cloned human (reproductive cloning).

Of the ethical criteria reflected in fundamental legal norms[167] and in medical ethics, objectives such as the reproductive cloning of humans and intervention in the human cell line must be regarded as ethically unacceptable. Reproductive cloning aims to give rise to a human possessing the nuclear genome of an individual already born, and therefore subordinates this

[167] Cf. 2.1.2 The objectives of research in human stem cells.

human being to the ends of third parties in a manner contrary to human dignity.[168] Interventions in the human germ line are associated with uncontrollable risks and require for their introduction experiments in humans that cannot be justified. They interfere with the genome of an unforeseeable number of future carriers of this genome without their consent. This is an act of predestination with regard to the individuals affected that cannot be legitimised even by a possible therapeutic objective. Stem cell research relating to procedures such as reproductive cloning and germ line intervention is accordingly to be rejected purely on the basis of its objectives, as medically and ethically unjustifiable

2.1.3 The means used in research in human stem cells

The high priority of the objectives pursued by stem cell research does not answer the question of the ethical justifiability of the means used. Even a high priority objective cannot justify ethically reprehensible means. Since modern technologies represent complex combinations of objectives and means, assessment of the means must take account of its function within such overall circumstances. Moreover, it must be borne in mind that a technology developed as a means within a particular set of circumstances can generally be used to achieve further objectives not intended at the time of its development.

The question of ethical justification of the means used in stem cell research relates in particular to the methods by which the stem cells required for research are obtained. The derivation of stem cells from human embryos is again the main focus here from the ethical point of view; the rights to protection attributable to the human embryo must be considered here and the consequences for society's dealings with unborn human life taken into account.

Since a variety of ethical viewpoints are found within society in the assessment of the worthiness of protection of the human embryo, the question of justifiability of the removal of stem cells from human embryos also meets with controversial responses. An ethical evaluation of research in stem cells derived from embryonic tissue is therefore impossible without recourse to the various views held with regard to assessment of the moral status of the human embryo, particularly during its very early stages of development, in order then to examine which ethical convictions are relevant in law and in amendment of the law.

2.1.4 The moral status of the human embryo: two fundamental positions

The question concerning the moral status of the human embryo relates to the basis, scope and beginning of its worthiness of protection. Determination of the status of the embryo created in vitro in the initial phase of its development, i.e. up to the formation of the primitive streak and

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[168] Cf. 3.1.1.3.3 Ethical assessment of the derivation of pluripotent embryonic stem cells by "therapeutic" cloning.

nidation in the uterus, is a particularly controversial matter. A variety of basic views can be found in our society, independent of the view on which our legislation is based, to be discussed below. These views differ as to whether the protection of human dignity applies even at this early phase, i.e. giving the embryo as such and independently of evaluations by third parties unlimited protection from the beginning of its existence, or whether it should have the status of an *extrinsic* object of protection, i.e. based on the assessment of third parties, or whether its own status as an object worthy of respect and protection depends on the degree of its development.

2.1.4.1 Position I: The human embryo is entitled to protection of human dignity from the beginning, i.e. from the completion of fertilisation

Position I is based on the fundamental value judgement that human dignity is ascribed to the human being from the very beginning. Human life is therefore exempt from any balancing of objects of value. Its claim to protection is limited only by claims to protection of the same order. In this sense, dignity is characteristic of the human being because he is capable, as the subject of his actions, of taking responsibility. If moral claims are not to remain unallocated, the subject who is capable of setting his own goals and pursuing them must be regarded as one who, as Immanuel Kant expressed it, constitutes an "end in itself" and must therefore be protected from any instrumentalisation that runs counter to this self-determination.

However, it is the human being who is capable, by virtue of the affirmation of human dignity, of being a moral subject. If one assumes that "human being" and "subject" are identical in nature (*identity criterion*) and if one further follows the human rights thinking that the protection of dignity should be dependent on nothing apart from the fact of being human, then any human individual must be worthy of the protection implied by the word dignity.

Moreover, since the human being delivered at birth shows unbroken continuity with the unborn human being from which it develops (c*ontinuity argument*), position I concludes from this that the worthiness of protection of the human being after birth must be extended to the unborn human. The question of the point to which this continuity and identity with the unborn individual extends, does indeed remain to be answered. Position I regards this point in time as being at the start of development of human life and sees this start as the point at which, after the two haploid sets of paternal and maternal chromosomes unite in the fertilised egg, a new living being is created with its own individual genome that determines its further development. In this case, fertilisation itself is regarded as a process occurring in the form of a cascade and seen as completed with the formation of a new individual genome.

If completion of fertilisation results in the creation of a new living individual with the real capability as such of developing into a human being who has been born (*potentiality argument*), and if this development encounters no caesuras that offer alternatives for

commencement of the inherent human worthiness of protection, then this worthiness of protection must be attributed to the embryo from the point of completed fertilisation. Any other determination of the beginning of worthiness of protection would be open to the objection of arbitrariness and would contravene the prohibition contained in human rights concepts, that worthiness of protection of the human being should not be made dependent on any criterion other than that of being human. For this reason, Immanuel Kant also did *not* make the actual exercise of reason a prerequisite for the attribution of dignity; for Kant, possession of "Menschheit" (humanity) is sufficient, i.e. possession of a human nature equipped with the ability to reason, peculiar even to the unborn human being.

With the concepts described, those who support Position I assume that the unassailable nature of the dignity ascribed to human beings and the protection of life are closely related. If in fact life in the womb is the condition for the ability to become a moral subject, the protection of life follows from the protection of dignity, and this also applies to the human embryo in its early stages. This may of course lead to the question of whether an offence against the protection of life also represents in all cases an offence against dignity, or whether a distinction can be made between the two claims for protection.

This distinction is represented by a **Position I/II** situated between Position I and Position II to be discussed below, which states that a human life as such –meaning from completion of fertilisation onwards – is entitled to the protection of dignity, irrespective of whether this life is yet to be regarded as the holder of rights. This protection of dignity cannot be balanced against any other objects of value. According to Position I/II, the same does not apply with regard to the requirement for protection of life. This view assumes that the requirement to protect life strengthens and the necessary level of protection rises with the progress of development towards birth. In the sphere of natural creation, this view allows for the acceptance and justification of a graduated change from the absence of legal protection prior to nidation to a growing worthiness of protection as the pregnancy advances.

In ascribing moral status and worthiness of protection, from the perspective of the first position, the question also arises as to whether the human embryo is to be regarded as the holder and subject of rights at the early stages or whether protection is due to it solely because, in view of its identity and continuity with the subject worthy of protection, it is itself worthy of protection.

A possible objection to Position I is that the moral status and the associated worthiness of protection can only be ascribed to a human individual, and that such an individual exists only if the stage has been reached at which the development of a multiple pregnancy is excluded. This objection is, of course, countered by the fact that, even before the possible formation of a multiple pregnancy, the embryo is without doubt already a genetically individual living creature of the human species.

The objection that Position I amounts to “speciesism”, because the only criterion for ascribing protection is that the unborn human is a member of the same biological species and therefore one biological species is being marked out unjustifiably above others, fails to distinguish between the *reason* and *criterion* for ascribing such protection. In fact, it is the capacity for subjectivity (Subjektseins) (“development form of the subject” (W. von Vitzthum)), associated with the nature of human life on which this special moral status is based and it is the fact of being a human being that acts as the criterion for allocating this status in accordance with Position I.

For determination of the moral status of the human embryo in vitro, the question arises as to whether the cell created by transfer of a somatic cell nucleus into an enucleated egg cell is to be regarded as a human embryo and whether the same status is attributable to it from the time of completion of transfer as to the fertilised egg cell, particularly in view of the wording of the Embryo Protection Act, which defines the term ‘embryo’ only as the human life form arising from combination of the two haploid sets of chromosomes of the egg and sperm.[169]

In response to this question, some argue that the creation of a cell type by cell nuclear transfer goes beyond our notions of human reproduction in which the biological, personal and social circumstances are connected. It is true that the cell type created has the ability to develop into a complete individual, but - at least up to the time of implantation – it has no parents to safeguard it. Nor is it embedded in a biographic context, so the world-wide consensus is that human reproduction by means of cloning, i.e. without being embedded in the context mentioned, violates human dignity and can therefore not be permitted.

According to the position in question, two reactions are possible to removal of the connection between totipotency and reproduction associated with the method of cell nuclear transfer: firstly, a total ban to protect this connection in accordance with human dignity or secondly, the conclusion that the cell created by cell nuclear transfer lies outside the context of reproduction so that other rules apply, such as those forbidding reproductive cloning but possibly under specific conditions permitting "therapeutic cloning".

The objection to the last alternative mentioned from the viewpoint of position I is that, in the case of humans, the connection between the living being and the capacity for subjective responsibility is so close that context and linking with a specific purpose are not sufficient argument to justify their separation. The fact that status is not so fundamentally changed by linking with a purpose as suggested by the last alternative is clear particularly from the fact that a cell created by cell nuclear transfer can develop, after implantation at any time, into a human being who has been born, so that in principle this exhibits potentiality, continuity and identity

[169] Cf. 1.2.3.1 Embryo Protection Act (ESchG)

with such a human being which, from the viewpoint of position I, confers on it the moral status of an embryo with the consequent protection of dignity and life.

2.1.4.2 Position II: Worthiness of protection is ascribed to the human embryo in a graduated way

Position II assumes that the full worthiness of protection due to the human being as a subject and person does not arise until a particular stage of the human being is reached, and that worthiness of protection of a secondary nature is due to the human embryo, at least in its early stages of development. Here again, a distinction must be made between a radical and a gradualist position.

The **radical form of position II** assumes that only a human being to whom certain characteristics are attributable, as acquired by the human being in the course of his development, is to be regarded as a person and accordingly as worthy of protection. Differences arise between those supporting this position in identifying the characteristics which constitute the person: If one assumes that rights are ascribed and presupposes that only a human living being who has interests and is aware of their violation can be the holder of rights, then the right to life begins only with possession and perception of such interests. The same applies if one bases the claim to respect by third parties on acquisition of the capacity for self-respect. If - to mention another approach - the basis for worthiness of protection is seen as the development of preferences of interests and awareness of these, and if only individuals who are capable of developing such interests are regarded as persons, then only those human beings capable of developing such preferences of interests, such as self-awareness, a concept of the future, etc. are regarded as persons; only as persons in this sense are they covered, according to this view, by a generally applicable prohibition on killing. Humans who are not persons are therefore worthy of protection only to the degree to which they – like other forms of life – possess interests at a simple level, such as the interest in avoiding pain.

The fundamental objection to this radical form of position II, according to its critics, is that it does not comply with the requirement of human rights concepts, that the moral status due to humans and the resulting worthiness of protection should not be made dependent on any characteristic other than that of being human, and therefore that it does not assume a corresponding fundamental ethical and legal equality of all humans. It is this basic principle of the European declaration of the fundamental equality of all human beings, say the objectors, that led to establishing the consequent protection in law and – as in Prussian common law – also relating it to the unborn human being. A link between human rights protection and the current possession, beginning only after birth, of particular characteristics would fall below this historic legal reference line and its underlying central judgement. From a viewpoint that links human rights protection to the existence of certain characteristics, even the attempt to

introduce human rights protection when birth at least has taken place could be postponed, since it would result in an unjustified rigidity contrary to this view.

The above objections to the radical form of position II make it clear why this view is regarded as discriminatory, particularly by those people who, because of disability or illness, might be able to lay only limited claim to those characteristics which the representatives of position II see as fundamental to the application of full worthiness of protection.

The **gradualist form of position II** assumes that the human being deserves protection from the point of completion of fertilisation, but that the degree of this worthiness of protection follows the stages of development through which the unborn human life passes after fertilisation is completed, and that the full extent of protection, as connected with the entitlement to human dignity and with the unassailable right to life, is applicable only when a certain level of development is reached. Relevant milestones in development are seen as follows: beginning of acquisition of form with development of the primitive streak, the exclusion of natural multiple pregnancy and the associated final individuation, nidation in the uterus, the development of the neuronal prerequisite for conscious processing of stimuli (start of cerebral life), the ability to survive outside the uterus etc. Particular importance is attached here to the first two characteristics mentioned insofar as they relate to the difference between the embryo in vitro and in utero and to the point in development reached approximately 12 to 14 days after fertilisation is complete .

The gradualist position is based on the progressive nature of becoming a human being, but – like many gradualists positions – in the opinion of its critics is subject to the fundamental objection that each morally relevant milestone marked within a continuous process is necessarily arbitrary and it is therefore clearer if the indisputable beginning of the continuous development of the embryo with completion of fertilisation is regarded as morally relevant and not one of the later stages of development. This is reinforced by the requirement of human rights principles, as mentioned above, that the worthiness of protection of human beings is to be made dependent on nothing but the fact of being a living human being.

On the other hand, the objection made to the gradualist position may be countered by the fact that even forms of position I contain elements of a decrease in protection such as acceptance of the dying of embryos when a number of embryos are implanted during IVF, or rejection of the donation of embryos that cannot be transferred to the woman concerned.[170]

2.1.4.3 Perspectives of feminism and relational ethics

The objection to the view of the embryo as an individual living being and as such worthy of protection, on which the two positions described are based, is that it shows unacceptable

[170] Cf. 3.1.1.2.3 Embryo donation and adoption.

disregard for the social relationships within which the embryo is located and through which it acquires its worthiness of protection.

From the *feminist perspective* it is pointed out that an evaluation of the embryo as an independent object of protection places the embryo in opposition to its mother and fails to take into account both the social experience of the woman and also the connection of the embryo with its mother. This one-sided attitude is reinforced by separation of the embryo in connection with IVF, which ascribes to the embryo an independence that does not concord with reality, makes pregnancy seem like a production process and degrades the woman to the supplier of egg cells. Only if the embryo is considered as a relational unit with its mother and the subject status of this unit is appropriately taken into account, the objection claims, is appropriate assessment of the status of the embryo possible.

From the perspective of *relational ethics* encountered in various forms, centring of ethical consideration on the individual subject is countered by the fact that individual identity is constituted only in the social context and that its worthiness of protection cannot be properly determined without this context. According to E. Lévinas, it is the countenance of the other from whose gaze the claim to moral respect first arises. According to Lévinas, the encounter with the other gives rise to a special responsibility to understand and accept the other in his strangeness, ambivalence and his physical and mental vulnerability. In this sense human dignity can be experienced in the encounter with the other person and is invariably the threatened dignity of the other. An ethic that isolates the autonomy of the subject and makes it absolute, can from this viewpoint therefore not be valid as a suitable explanation of the ethical claim.

Without doubt, the *social relational network* in which the human being is born, develops and gains his self esteem as a subject is a dimension of particular significance for the generation and also the realisation of ethical claims. If one assumes the concept of human dignity and human rights under which each human being deserves protection irrespective of his social acceptance by third parties, this concept requires the social network to be taken into account in which the claims to protection articulated with the concepts of human dignity and human rights are expressed and validated. This means that relational ethics are to be regarded as a perspective without the consideration of which the question of the moral status of the embryo can be answered only in curtailed form.

2.1.5 The moral status of the human embryo: agreements and differences

As is clear from this brief description, the positions differ with regard to their central concepts, which explains why the intensive discussion concerning the moral status of the embryo, as it has taken place in connection with the problems of termination of pregnancy in western societies, has so far led to no convergence of views within society. In the German debate in particular, position I and the moderate gradualist form of position II have been of particular

social relevance, though not the radical form of position II, which – as the reasons shown above have made clear – contravene the principles of human dignity embodied in constitutional law. In addition to the *differences* outlined between position I, I/II and the moderate gradualist form of position II, there is also *common ground*, at least for some of those supporting the latter position. Determination of the extent of this common ground is important particularly where it is necessary, in societies characterised by the above dissension concerning the moral status of the embryo, to find legal regulations that conform to human rights concepts and the fundamental ethical convictions expressed in the basic principles of constitutional law.

2.1.5.1 Areas of agreement

The common ground for the last positions mentioned is that they regard the *beginning of human life* as being completion of fertilisation, that they ascribe worthiness of protection to this human life from the beginning and accordingly regard human life as something that may not be treated arbitrarily at any point in its development. This expresses the basic moral conviction that human life has a value that is independent of recognition by third parties and therefore as such is deserving of protection. This basic intuition is found in the context of specifically religious convictions (such as that of the *sanctity of life*) and is supported by them. However, this intuitive perception is also regarded as binding by those who do not share these religious convictions. It evidently has a plausibility that is not necessarily bound up with religious premises. A similar distinction can also be seen with regard to the deeper philosophical reasoning, whether arising from metaphysics or historical philosophy. Only a distinction of this kind makes it understandable that human rights thinking, irrespective of its historical origin in antiquity, Judaism, Christendom or European enlightenment, has at its core found world-wide acceptance, crossing the boundaries of various cultures, and has also not been lost in the differences of interpretation.

This is evident – as indicated by Ronald Dworkin – in the debate taking place in modern societies, where termination of pregnancy and active euthanasia are regarded as requiring justification even by those who represent different views with regard to the degree of worthiness of protection of human life. “Almost everyone expressly or intuitively agrees with the concept that human life has value in itself that is quite independent of its personal value for any individual.”[171] To rob human beings by killing them of the opportunity “to live a life like our own”[172] clearly contravenes one of the fundamental moral convictions.

Central and generally shared *moral perceptions*, such as the above intuitive perception concerning the inviolability of human life, are in no way divorced from the question of the reasons for these, as posed by ethics and jurisprudence. Conversely, ethics and jurisprudence

[171] Dworkin 1994, P. 98.
[172] Holm 1998, P. 42.

are bound to take account of the weight of central moral perceptions and to give evidence of their deliberations as a reconstruction of the universally accessible moral judgement. Not without reason, therefore, do basic ethical theories assume that the reflective ethical process of reaching judgement in this respect takes the form of a "balance of considerations" (John Rawls).

2.1.5.2 Differences

The *substantial differences* between the two last named positions are evident with respect to the balancing process in the event of competing objects of value: according to the gradualist view, a balancing of the worthiness of protection of the embryo in its early stages of development with regard to high-priority objectives appears justifiable because the embryo at this stage of development need not be regarded as having the full moral status ascribed to it at later stages. For representatives of position I, a balancing process is either completely excluded or legitimate only in the event of conflict between two objects of the same high value that cannot be resolved in any other way.

As is clear from the review of the various positions held on the moral status of the human embryo in vitro and the consequent worthiness of protection, with their common ground and differences, no agreement is to be expected in the medium term which could lead directly to the necessary legislation. However, since legal regulations must be put in place, the question arises as to what partial consensus can be used as a basis. In determining this consensus, the ethical convictions expressed in the standards set out by constitutional law play a decisive role. Since they also represent the starting point for the legislators for legal regulation of the field in question, the following section will examine the status and worthiness of protection enjoyed by the human embryo under German constitutional law.

2.1.6 The question of assessment of moral status of the human embryo under Basic Law

The latitude available to legislators when deciding and drawing up regulations for stem cell research is determined by the provisions of constitutional law. The aspects concerned in embryo and stem cell research are the basic right of freedom of science and research under Art. 5 (3) sub-section 1 GG[173] on the one hand and protection of human dignity under Art. 1 (1) GG[174] and the right to life and physical inviolability under Art. 2 (2) sub-section 1 GG[175] on the other.

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[173] Art. 5 (3) sub-section 1 GG: "Art and science, research and teaching are free."
[174] Art. 1 (1) GG: "Human dignity is unassailable. It is the duty of all State powers to respect and to protect this."
[175] Art. 2 (2) sub-section 1 GG: “Every individual has the right to life and freedom from injury."

The freedom of science and research relates to a human "original process", the creativity of creative thought, enquiry and action as the expression of human uniqueness and dignity. At the same time it has a social aspect, as the basis of the progress of civilisation, technological development and socio-economic welfare in the community.[176] The guarantee of freedom of science and research is a classical right of defence against the state. In it is expressed the interest of society in the progressive process of gaining information. The basic right of freedom to research therefore also basically refuses the state the right to try to determine the purpose and objective of research projects.

The freedom of science and research is guaranteed without reservation. Limitations in the exercise of this basic right are permissible only insofar as they arise from the constitution itself. The concrete application of constitutional limits is the task of the legislators, who must find a balance between the competing objects of value protected by basis rights. Insofar as it is necessary to protect other basis rights, the legislators may therefore limit the freedom of science and research by means of orders and prohibitions. This was the case, for example, with the Embryo Protection Act of 13 December 1990.

The legal limits of embryo and stem cell research are closely related to the constitutional status of the embryo in vitro. Is it the bearer of basic rights, by which constitutional legal norms is it protected and to what extent do its basic rights take precedence over the freedom of research and science?

Fundamental to the constitutional legal status of the embryo in vitro is the response to the question of the extent to which, and from which point in time onwards, the embryo in vitro enjoys the constitutional legal protection of life under Art. 2 (2) and of human dignity under Art. 1 (1) GG.

The wording of Art. 1 protects the dignity “of the human being” and Art. 2 states that, “every individual” has a right to life. The Federal Constitutional Court, however, decided that the protection of dignity and life provided by the Basic Law is limited not only to human beings after birth or to the independently viable individual about to be born, but also to unborn human life.[177] Without doubt this core statement was a main basis for decisions by the Federal Constitutional Court on this matter, so that it forms part of the binding effect of Art. 31 of the Law of the Federal Constitutional Court (BVerfGG)[178].[179]

[176] Pernice 1996, note 13 with further references.
[177] Decision by Federal Constitutional Court (BVerfGE) 39, 1 ff., Statement of principles 1; BVerfGE 88, 203 ff., Statement of principles 1.
[178] § 31 (1) BVerfGG reads "The decisions of the Federal constitutional court bind the constitutional organs of the Federation and of the regions and all courts and authorities."
[179] Sacksofsky 2001, P. 7 with further references.

The radical form of position II[180], as described above, though it plays a part in the philosophical debate, is therefore fundamentally excluded as an option for decisions by the legislators.

However, this does not clarify the question of the extent to which, and from which point in time, the embryo created outside the body in vitro begins to enjoy the protection of basic law.

In the literature on law and legal philosophy, a wide variety of views are represented concerning the question of the time from which the unborn life begins to enjoy the protection of basic law. Jurisprudence, however, assumes almost unanimously that the protection of life under Art. 2 (2) GG begins with the merging of the egg and sperm cells.[181] Here again no distinction is made between the embryo in vitro and that in vivo. The reason given is that merging of the two haploid sets of chromosomes determines the genetic identity, uniqueness and immutability of the human being and its potential for development as a human being and that, in view of the continuity of this development, any other break point between the fusing of the egg and sperm cells and birth appears arbitrary.[182] This also complies with the scientific findings of modern embryology. The embryo, from the point of fusion of the nuclei onwards, is a functional, self-organising and differentiating unit controlled by its individual genome.[183] Nor is this contradicted by the fact that embryonic cells at this early stage can still be totipotent, so that in the event of division several embryos (identical multiple progeny) can develop. Here again, the individuality of the embryos is established from the point of nuclear fusion onwards. Anyone who takes the possibility of multiple pregnancy formation which still exists at this stage as a reason to deny the individuality of the embryo created by fusion of the egg and sperm cell is confusing individuality with singularity.

This point, fixed by constitutional law at the beginning of human life, is at the same time the starting point for a response to the question of the extent to which, and from when, the guarantee of human dignity for the embryo in vitro under Art. 1 (1) GG becomes effective.

The content and extent of human dignity guaranteed in Art. 1 (1) GG as a basic legal assurance are not clear in themselves, but require concrete definition.

According to the jurisdiction of the Federal Constitutional Court, human dignity is

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[180] Cf. section "2.1.4.2 position II: Worthiness of protection is ascribed to the human embryo in a graduated way".
[181] Account by Höfling 2001a, P. 47-50 with further references.
[182] Höfling, 2001a, P. 50 f. with further references; Sacksofsky 2001, P. 11 f. with reference to the grounds for decision of BVerfGE 88, 203 ff.
[183] Bodden-Heidrich et al. 1998, P. 15 ff.

> the claim to social value and respect.... that prohibits the human being from being made simply an object of the State or being subjected to behaviour that in principle calls into question his quality as a subject. Human dignity in this sense is not the individual dignity of the person concerned, but the dignity of human beings as a species. All persons have this dignity, without regard to their characteristics, their behaviour or their social status. It is also attributable to those incapable of sensible behaviour because of their physical or intellectual condition. Nor is it lost as a result of "unworthy" behaviour.[184]

All human beings, irrespective of their individual characteristics and capabilities, are therefore bearers of human dignity. No distinction is possible under constitutional law between human being and person. Human dignity is a status attributable to all human beings as such and cannot be lost. The protection of human dignity, according to this definition, also extends to the human embryo. All other break points would be arbitrary and would require interpretation. Particularly in the case of high-ranking objects of legal protection, in cases of doubt, according to the jurisdiction of the Federal Constitutional Court, that interpretation which most strongly exercises the legal effect of the basic legal norm is to be selected.[185]

The German constitutional court has also stated, in its two judgements concerning regulation of deadlines in termination of pregnancy: "Where human life exists, human dignity is attributed to it ...The potential capabilities present from the beginning in human existence are sufficient to justify human dignity".[186] This statement contains firstly a rejection of an understanding of dignity that allows someone the claim to protection of Art. 1 (1) only from a certain stage of physical, mental or moral development or maturity.[187] Secondly, the beginning of human life is therefore fixed as the point at which protection of human dignity begins.

In the judgements quoted, the German Constitutional Court did not deal with the question of the status of the embryo before nidation and therefore left open the extent to which the embryo in vitro also shares in the protection of human dignity. The judgements allow no statement to be made as to how the German Federal Court will judge the basic legal status of an embryo created in vitro.[188] In the explanation of the decision taken in the second judgement (1993), however, the German constitutional court stated:

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[184] BVerfGE 87, 209 (228).
[185] BVerfGE 32, 54 (71); 39, 1 (38); 48, 376 (388).
[186] BVerfGE 39, 1 (41) and 88, 203 (252).
[187] Höfling 1999, note 46.
[188] Limbach 2001, P. 6.

> The present case requires no decision as to whether, as seems likely from the knowledge of medical science, human life originates with the fusion of the egg and sperm cell. The subject of the regulation in question is the termination of pregnancy, in particular the criminal legislation; only the period of pregnancy is therefore important to the decision. This runs, according to the ... provisions of the criminal code, from completion of implantation of the fertilised egg in the womb (nidation ....). In all cases during the period of pregnancy determined in this way, the unborn child is an individual no longer divisible life, fixed in its genetic identity and therefore in its uniqueness and immutability, that in the process of growing and evolving is developing not primarily into a human being, but as a human being.... However the various phases of antenatal life processes may be interpreted from the biological, philosophical or even theological points of view and however they have been judged in history, these are in any case indispensable stages in the development of an individual human being. Where human life exists, human dignity is attributable to it. [189]

In the light of this broadly based concept of protection, the conclusion is often drawn that the logic of this judgement infers that its effects are not limited to the period of pregnancy, that is, from nidation, and that it cannot be assumed from this that the German constitutional court will make a radical change of course in such a central question.[190]

A positive definition of the content of human dignity has not yet been given; nor does it appear possible. Its content may rather be deduced from the concrete offence of its violation. Any attack on human dignity also constitutes an offence against it.[191] The constitutional court applies[192] in this area the much-quoted object formula of Günter Dürig:

> Human dignity is affected if the actual human being is degraded to an object, to a means to an end, to a replaceable value.[193]

although it is reticent in evaluating this object formula, which in turn is only the interpretation of a legal text: Not in every case in which human beings appear to be simple objects of an act is their human dignity necessarily violated. For it is not unusual for human beings to be merely the objects of others, society, or even the law. The object formula only indicates the direction in which crimes of violation may be found. The decisive factor should be whether the subject quality of human beings is fundamentally denied.[194]

Human dignity is “unassailable”, i.e. it applies absolutely. A balancing of objects of value with other basic rights or even limitation by laws is impossible. Art. 2 (2) subsection 3 GG[195], however, allows interventions in the right to life and physical inviolability – while preserving the essential content (see Art. 19 (2) GG). There are therefore some who wish to “shift” protection of the unborn life in general under basic law from protection of human dignity to

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[189] BVerfGE 88, 203 (251 f.).
[190] Benda 2001b
[191] Sacksofsky 2001, P 54 with further references.
[192] BVerfGE 72, 105 (116); 87, 209 (228); 96, 375 (396).
[193] Dürig 1972, note 28, 34.
[194] BVerfGE 30, 1, 25 f.
[195] Art. 2 (2) sub-section 3 reads: These rights may be modified only on the basis of a law.

protection of life, in order to provide for graduated solutions according to the stage of development of the human life[196], or to limit the protection of the embryo under basic law, at least for the time prior to nidation, to the right to life.[197]

Based on the assumption that the embryo in vitro has the constitutional right to protection of life in accordance with Art. 2 (2) sub-section 1 and the right to protection of human dignity, various conclusions are drawn regarding resolution of the cases of conflict under constitutional law arising as a result of stem cell derivation, the various fundamental convictions described in the previous sections concerning the ethical problems of stem cell research also being reflected in the dispute over the constitutional status of the embryo in vitro.

If it is assumed that a need to protect life also stems in principle from the absolute guarantee of human dignity for the embryo in vitro[198] (cf. also comments on position I[199] in the ethical assessment of worthiness of protection of the embryo), the derivation of stem cells from embryos in vitro would itself be unacceptable in view of the resulting deliberate killing of the embryo. Acceptance of a life-threatening or life-ending treatment would not constitute a violation of dignity only in extreme situations where life is weighed against life, as might be the case in situations of emergency or defence. This is not the case here. If it is assumed that the protection of human dignity and the protection of right to life are not completely congruent, a certain latitude of balance becomes available with regard to the right to life, though not to the guarantee of human dignity.

Interference in human life, irrespective of a latitude for balance provided under Art. 2 (2) GG is always prohibited, however, if it violates human dignity.[200] If one follows the arguments described under **position I**[201] in the ethical assessment of the worthiness of protection of the embryo in vitro, the derivation of stem cells from human embryos is an unacceptable interference in the human dignity of the embryo and is prohibited without exception, even if this results in foregoing the search for new types of treatment options. This applies to "supernumerary" embryos and – all the more – for embryos produced for research purposes.

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[196] Dreier 1996b, note 51 with further references.

[197] Hufen 2000. This view is also based on the recommendations of the German Research Association (Deutsche Forschungsgemeinschaft) on research with human stem cells dated 3 May, 2001, cf. Deutsche Forschungsgemeinschaft 2001a.

[198] The decisions of the German constitutional court on termination of pregnancy suggest this. The court calls life "the vital basis of human dignity", BVerfGE 39, 1 (42). In the 1993 decision, the basis of the State's obligation also to protect unborn human life stems from Art. 1 (1): This obligation to protect (i.e.: to protect human life – under the constitution) is founded in Art. 1 (1) GG, which expressly obliges the State to respect and protect human dignity; "its subject and ... its extent are defined in more detail in Art. 2 (2) " (BVerfGE 88, 203, Statement of principles 1 and sub-section 251). Also against: Sacksofsky 2001, P. 38.

[199] Cf. Section "2.1.4.1 position I: The human embryo is entitled to protection of human dignity from the beginning, i.e. from completion of fertilisation".

[200] Höfling 2001b, P. 8.

[201] Cf. section "2.1.4.1 position I: The human embryo is entitled to protection of human dignity from the beginning, i.e. from completion of fertilisation".

Under these circumstances the embryo is being used exclusively for the benefit of others and its subject quality is therefore fundamentally being called into question.[202]

For those advocating **position I/II**[203], who recognise human dignity for the human embryo from the beginning, but regard protection of life under certain circumstances as able to be balanced with other objects of legal protection, the requirement to protect life arising from the right to life may also be subject to limitations where it conflicts with other high-ranking objects of legal protection. Not in every case in which the legal system provides no absolute protection of life is this to be regarded as a violation of human dignity. The laws of the state must protect and promote all human life, generally also with criminal prohibitions.[204] In conflict with other high-ranking objects of legal protection, however, balance according to this point of view is an ethical and legal obligation.

The assumption that the intensity of the requirement for protection of life increases with advancing development of the embryo and is not fully in place with the earliest stages of development, as in the case of the embryo in vitro, is regarded by representatives of this position as constitutionally permissible. The derivation of human stem cells from human embryos relates to a procedure undertaken at a time when the requirement for protection of life, according to this position, has not yet reached its maximum expression. This is also supported by reference to the regulation of termination of pregnancy accepted by the constitutional court and the fact that coils[205] and “morning after” pills have not been regulated by the legislators (for the last two situations, in particular, it was not even possible to put forward cases in justification involving conflicts for a woman).[206] It is pointed out, according to one objection, but ignoring the existing differences, that one case involves the prevention of an opportunity of life which is extremely difficult to prove, while stem cell harvesting involves deliberate use of the embryo resulting in death.

Nevertheless, according to this position, the protection of life of every human embryo resulting from human dignity should have priority over an equally high-ranking legal right of third parties, if it can still be protected. Embryos referred to as "supernumerary", i.e. those created for the purpose of giving rise to a pregnancy in a woman whose egg cells have been fertilised in vitro for this purpose, but which can no longer be used for this purpose for reasons that

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[202] This is the conclusion reached by predominant teaching on the constitution, insofar as this recognises the basic right of protection of human dignity for the embryo in vitro, cf. e.g. Benda 2001a; Laufs 2000, P. 2716 ff.; Böckenförde 2001; Sacksofskfy 2001, P. 48; Höfling 2001, P. 218. The latter also regards the use of embryos for research purposes as breach of a taboo.

[203] Position I/II is described in section: "2.1.4.1 position I: The latter also regards the use of embryos for research purposes as breach of a taboo."

[204] BVerfGE 88, 203, (251/253 f.).

[205] According to Dr. med. Rolf Klimm, the coil does not, however, prevent nidation but conception (fertilisation), by inactivating the approaching sperm as a result of sterile inflammation of the endometrium of the uterus (Klimm 2001).

[206] Cf. on this subject: Sacksofsky 2001, P. 29.

relate to the woman and for which there is also no other prospect of achieving life, can no longer be guaranteed development to a complete human existence. Their worthiness of protection is therefore reduced to the possibility of being allowed to die. The decision concerning death must inevitably be taken by human beings. While no-one normally has the right to dispose of another human life, this decision can no longer be avoided in the case of "supernumerary" embryos. Since the decision concerning disposal in these cases does not represent a contravention of the dignity of the embryonic life, the representatives of this position therefore also regard the decision to use it as no such contravention. The objection here is that there is an ethically significant difference between action and omission. While omitting to implant the embryo into the body of a woman implies the unavoidable consequence that the embryo will die, by releasing it for stem cell harvesting the embryo is intentionally being used for purposes which benefit a third party and which intentionally lead to its death.

Advocates of the position described do not see the use of a "supernumerary" embryo for stem cell derivation as instrumentalisation, denying its characteristic as a subject, and therefore do not regard this as a violation of human dignity. An offence against human dignity would exist, for the representatives of this position, only if an act showed complete disregard for another human individual and his rights. The "object formula" repeatedly used by the constitutional court, as mentioned previously, only indicates the direction in which answers to the question may be sought as to whether human dignity is violated in a particular case. Anyone regarding the derivation of stem cells from "supernumerary" embryos as legitimate option in the sense described would not be representing any such attitude of disrespect and indifference with regard to human dignity. This position incorporates the absolute priority of every opportunity of life that an embryo might still have, including investigation of embryo adoption. The right to life would take priority over any use of an embryo for the benefit of third parties. Against this, one of the objections raised concerns the particular problems of managing this position in practice. Technically, the embryo could be cryopreserved even for decades, until a woman could be found for implantation and to carry the embryo to term.

Whether the decisions of the German constitutional court on termination of pregnancy imply a concept of increasing protection of life, as assumed by this position, is disputed by many. The Court itself states in its decisions that the degree of protection required by the constitution is independent of the stage of the pregnancy and that basic law allows for no grading of protection of the unborn life depending on certain dates.[207] Differentiations based on the particular stage of development of the human life are, however, compatible with equal protection of dignity in principle, insofar as they do not call into question life, the existential basis of human dignity.[208] The court finds that termination of pregnancy must be regarded as

[207] BVerfGE 88, 203, 254.
[208] Starck 2001, P 55.

wrong for the entire duration of the pregnancy and accordingly must be prohibited in law.[209] The regulations for termination of pregnancy drawn up by the Court assume the fundamental priority of the right to life of the embryo over the right of self determination of the woman. The purpose of the concept of counselling as a prerequisite for the legality of a termination of pregnancy, according to the German constitutional court, is the protection of the unborn life, the prevention of abortions with a concept that takes account of the unique connection between the woman and the unborn child ("duality in unity"[210]), for which no parallel exists in other aspects of life[211]. Underlying this concept is the understanding that protection of the unborn child, as required by law, cannot succeed without the heartfelt agreement of the woman and therefore that the decision not to implement protection of life by means of criminal law is required precisely for reasons of protection of life.

The contradiction in values claimed by many between regulations for termination of pregnancy reached under the decisions of the German constitutional court and the prohibition of research in embryos is to this extent not the case.[212] The legality of termination of pregnancy is possible only on the basis of the interests of the woman, protected under basic law, which are so serious that they can outweigh the basic right of protection of the unborn child.[213] A decisive criterion is the "unreasonableness" of continuing with the pregnancy, which results for the woman in enormous physical and mental changes. Correspondingly weighty reasons to those which a woman can invoke for a termination in the event of unreasonableness of the pregnancy, cannot be invoked for the killing of the embryo in vitro. A comparison with termination of pregnancy is therefore not permissible. The reasons for allowing embryo research must therefore be justified rather by the subject of the research itself and the objectives in question.

If the derivation of embryonic stem cells is considered from the point of view of protection of life only (Art. 2 (2) P. 1 GG), the following emerges: Since the protection of life required under basic law begins with fusion of the egg and sperm cell, the use of embryos for the derivation of stem cells undoubtedly constitutes an interference in the right to life and freedom from bodily injury under Art. 2 (2) GG.

Within the regulations of basic law, human life represents a maximum value[214]. For this reason, only particularly high-ranking reasons can allow any intervention in the right to life to appear justified. For the embryo it is "all or nothing", a matter of its biological and physical existence guaranteed to it by its right to life under basic law. Therefore, also on the basis of Art. 2 (2)

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[209] BVerfGE 88, 203, Statement of principles 4 and BVerfGE 39, 1, 44.
[210] BVerfGE 88, 203, 253.
[211] BVerfGE 39, 1, 42.
[212] Cf. on the following Sacksofsky 2001, P. 30-32.
[213] The objects of legal protection affected by the right to life of the unborn child here are – based on the claim of the pregnant woman to protection and respect for h e r human dignity (Art. 1 (1)) – in particular her right to life and freedom from bodily harm and her individual right (Art. 2 (1)) (BVerfGE 88, 203, 254).
[214] BVerfGE 39, 1, 42.

GG, the legal regulations allow acts resulting in death only in extreme exceptional cases, that is, where only in this way can the life of another human being be saved or an illegal attack be prevented[215]. These conditions are not fulfilled in the case of research in embryos.

The view that the right to life of actual human beings, who could possibly be saved from life-threatening danger or serious risk to health in the near future, could be weighed against the requirement to protect the life of embryos is not adequately justified by the present state of research. Much of what is being done within the sphere of stem cell research is still directed towards the gathering of fundamental information, the usefulness of which for therapeutic purposes has still to be demonstrated.[216]

From another viewpoint, interference in the right to life is also permissible if other high-ranking objects of legal protection are also at stake.[217] This corresponds in effect with the **gradualist** variant of **position II** mentioned above.[218] According to this, the balancing of objects of value would not require actually diseases to be named in which an opportunity of improving the chances of a cure could be expected in the near future. Basic research would form part, rather, of the attempt to increase the competence of the medical sciences for the benefit of patients. According to this view, the interests not only of present but also of unknown future patients is sufficiently important to outweigh the right to life of the embryo in vitro in the balancing process. However, even those who hold this view assume overwhelmingly that these conditions are fulfilled at present only with the use of "supernumerary" embryos.

When defining the basis for all views that regard balancing of priorities as acceptable, the constitutional legal principle of proportionality must be taken into account. In view of the high priority of human life within the context of basic law, an essential prerequisite, in limiting the right to life for the derivation of stem cells from embryos, is the actual demonstration that the use of such "supernumerary" embryos is appropriate and necessary in order to achieve the high-priority research objectives concerned, particularly with regard to alternatives which may exist, such as the use of animal material and research using adult stem cells.

2.2 Constitutional right to treatment

The only counterbalance to the fundamental right to the protection of human dignity and the protection of life under Art. 1 (1) and Art. 2 (2) is the freedom of science and research in accordance with Art. 5 (3) GG. With respect to research in embryonic stem cells, the research concerned is not (only) relying on an abstract interest in the obtaining of new information, but

[215] Examples: Defence, police rescue. Cf. Kunig 2000, note 85; Murswiek 1999, note 182; Benda 2001a.
[216] Cf. 1.1.2.1 Therapeutic application; 1.1.3. Expected future developments and Appendix I.
[217] Sacksofsky 2001, P. 24, who, however, assumes violation of human dignity and therefore finally reaches the conclusion that embryo and stem cell research, even in "supernumerary" embryos, is not permissible.
[218] Cf. Section "2.1.4.2 position II: Worthiness of protection is ascribed to the human embryo in a graduated way".

also on the interest of previously incurable diseases in the development of new treatments. The promise of cure and alleviation from the new treatment opportunities expected from research in embryonic stem cells plays a greater role in the public discussion concerning approval of research using embryos than any call for the freedom of science and research. Beyond the indubitable political and social significance of these arguments, the degree of admissibility under basic law of a claim to the development of certain treatments, that is, a subjective legal claim to a specific service from the health system, and consequently a State obligation to develop or make available the appropriate framework conditions for the development of such a treatment, must be clarified.[219]

Of undisputed significance in principle for the questions under discussion is the welfare state principle embodied in Art. 20 (1) and Art. 28 (1) GG. In established practice, the German constitutional court infers from this state structural norm the objective legal obligation to ensure the medical care of the population. This obligation is met by the State by the provision of state and public hospitals and legal systems of regulation, such as social security legislation. However, it is the inevitable consequence of its public and pragmatic regulatory structure that the principle of the welfare state cannot make concrete provision for decisions concerning the supply of funds for the health service at the macro-allocation level.[220] While the State provides for a public health system that is not obviously defective, it is acting within the normative framework laid down by the welfare state principle under basic law. Regarding the level of funds to be made available and assessment of the level or standard of a health system, the State has a far-reaching prerogative for judgment.[221]

The welfare state principle as such exerts its – extremely limited, as shown above – normative power of direction, however, only as an objective legal principle. Subjective legal positions, i.e. claims by individuals, are not supported by this principle in itself. To this extent, however, the guarantee of human dignity under Art. 1 (1) GG may provide the link between objective legal obligation and subjective legal claim. According to the jurisdiction of the German constitutional court, Art. 1 (1) GG should "in all cases ensure the minimum requirements for a dignified human existence".[222] However, the German constitutional court, in a recent decision, gave an open verdict as to whether Art. 1 (1) GG did actually confer a subjective right in this respect.[223] Even if this question is – appropriately – answered in the affirmative[224], the "human

[219] The comments below are taken from: Höfling 2000.
[220] Cf. also BVerfGE 144, 353 (375); 57, 70 (99); 67, 193 (209, 220); 68, 193 (218); BVerfG, MedR 1997, 318 f.
[221] Cf. also in summary: Künschner 1992, P. 264 ff.
[222] Cf. BVerfGE 40, 121 (133); 48, 346 (361).
[223] BVerfGE 75, 348 (360).
[224] For details of the content of the subjective legal guarantee of human dignity with regard to legal performance, see Höfling 1999, note 19 ff.

dignity component" of the law relating to services provided by the State is limited to a residual core.

The same applies to the guarantee of Art. 2 (2) sub-section 1 GG often referred to in the present context. In this connection, a far-reaching multifunctional dimension is often attributed to the right to life and freedom from physical injury in the sense of a claim to (sometimes even the best possible) medical care, though without adequate dogmatic foundation for this claim.[225]

In a decision concerning the obligations of the statutory health insurance bodies to provide services, the German constitutional court stated:

> It is true that Art. 2 (2) sub-section 1 GG guarantees free self-determination of the patient with regard to medical interventions with the result that the patient alone is entitled to the final decision concerning the treatment to be applied in his case. However, this does not give rise to any claim under constitutional law against the health insurance bodies to make available the appropriate medical care and to the guarantee of financial funding for this. A claim to be lodged on the basis of unconstitutionality, that specific health services should be kept available that cure disease or that in any case result in diseases not being aggravated further cannot be inferred from Art. 2 (2) sub-section 1 GG. An objective legal obligation of the State does arise from Art. 2 (2) sub-section 1 GG to take protective and promoting action with regard to the object of legal protection of Art. 2 (2) sub-section 1 GG. Interpretation of the relevant law concerning statutory health insurance must also be based on this. A claim under basic law associated with this protective obligation is, however, in view of the freedom of organisation given to the state bodies concerned in the fulfilment of the protective obligation, implies only that the public authority must make arrangements which are not wholly unsuitable or wholly inadequate to protect that basic right. Only within these limits can the German constitutional court examine fulfilment of the obligation to protect.[226]

A subjective legal claim to a particular treatment, in this case stem cell therapy, is therefore not justifiable. An obligation by the State under constitutional law to develop such treatment or to create the basic conditions for such a treatment, which must be weighed against the various other objects of value to be protected by basic law, does not exist.

In any case, by promoting research in adult stem cells, the State would be meeting its obligations arising from the welfare state principle to an adequate extent.

Even if a subjective legal claim to the provision of particular treatments were justifiable, this could not extent to those treatments for which interference in the right to life of others was a prerequisite.

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[225] Cf. for example Däubler 1972; Francke 1994, 72ff; in general Seewald 1981.
[226] According to BVerfG, MedR 1997, 318 (319) with reference to BVerfGE 77, 170 (215); 79, 174 (202).

2.3 Informed consent under constitutional law[227]

The right of self determination of Art. 2 (1) and the right to life and freedom from injury under Art 2 (2) sub-section 1 GG also incorporate physical integrity. It follows that the use of bodily substances, even in the smallest quantities, is permissible only on the basis of specific and informed consent of the (former) bearer of the substance. In view of the "depth" of personal rights relating to all human bodily substances, each act of use and disposal following removal/harvesting requires **informed consent** specifically relating to this act from the bearer of the substance. Consent to a diagnostic or therapeutic medical procedure therefore does not imply authority with regard to the further disposal of the human biological material obtained in this procedure. The regulations based on rights of ownership relating to general use and disposal do not apply. These are overridden by personal rights legislation. This is more particularly the case for dealings with germ cells, where jurisdiction and the legal literature also result in subordination of rights of ownership to personal rights.[228]

Informed consent is consent given voluntarily after the fullest possible provision of information. If a scientist or doctor wishes to use or pass on bodily material for scientific, therapeutic or commercial purposes, e.g. for a patent, he requires the documented, purpose-related informed consent of the person from whom the bodily substance originates or from his or her legal representative. The absence of informed consent leads to the strict prohibition of derivation and use.

It is the task of the legislator to regulate the requirements, scope and extent and also questions of data protection legislation for the implementation of personal rights in this area and the legal consequences in the event of absence of informed consent. Informed consent is not sufficient justification for the use of embryos since these, as bearers of their own basic rights, are not subject to the power of disposal of their parents.[229]

2.4 Quality assurance and monitoring

Stem cell research, like any other research, is subject to quality assurance measures. These comprise careful, scientifically verified procedures as well as comprehensive statistical evaluation and publication in scientific media. Publication is necessary in order to allow critical debate of the research findings achieved and at the same time the most rapid and reliable broadcasting possible of the information obtained.

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[227] Höfling 2001a, P. 136 ff.
[228] Höfling 2001a, P.151 ff. with further references.
[229] Cf. Höfling 2001, P. 173.

For stem cell research in association with clinical use or research in human volunteers, further demands must be made, taking account of the quality requirements of the medical structure (qualifications of researcher concerned) and also the quality of the process and findings and particularly protection of the volunteer.

Since the various types of stem cell use have for the most part involved new kinds of treatment concepts, in which competing approaches are still giving rise to ethical concern, central monitoring of stem cell use is desirable at least for some areas of stem cell research – insofar as monitoring in the sense of clinical drug trials is not in any case required. Central monitoring could both protect volunteers and control misuse and also constitute a valuable data source for assessment of the consequences of technology and for the preparation of health reports.

3 Embryonic stem cells (ES cells)

3.1 Ethical and legal problems

3.1.1 Derivation of ES cell lines

Embryonic stem cell lines can be derived:

- from embryos in vitro, created specifically for this purpose.
- from embryos in vitro, created for the purpose of bringing about a pregnancy by IVF and for which, for a particular reason associated with the woman[230], transplantation into the uterus of the woman is no longer possible.[231]
- from pronuclear stages that have been cryopreserved during IVF procedures and that are not yet embryos on the basis of the definition of § 8 (1) ESchG but could be developed to embryos within a short period and which, for the reasons mentioned above or because family planning is complete, are also not to be used to give rise to a pregnancy.
- by means of "therapeutic" cloning.

In Germany, because of the ban on producing embryos except for the purpose of giving rise to a pregnancy[232], the existence of embryos produced for research purposes is illegal. The Embryo Protection Act also prohibits cloning techniques.[233]

Even if the ban on production of embryos for purposes other than to give rise to a pregnancy is observed, it may be the case that, for a reason associated with the woman, the three[234] embryos normally produced within an IVF procedure are not transferred into the woman's uterus. This may not be a temporary situation, but may be permanently the case. Therefore, in spite of compliance with the law, "supernumerary" embryos may exist. A valid legal definition, however, has not yet been prepared as to when (period of storage) and under what conditions (authorised persons, informing of donors) an embryo is to be regarded as "supernumerary". There are three options for dealing with these, as described in the next section.

A change in IVF procedures, limiting the number of embryos created from three to one, does reduce the mental and physical burden on women, in so far as only one egg cell is taken

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[230] For example change of mind, illness or death of the woman.

[231] These embryos are described as "supernumerary" embryos in the following text. The use of the terms "orphaned" (as in the terminology of the federal government in response to the major interpolation from FDP delegates concerning the need for a broad public debate on "therapeutic cloning" on 30 May 2001. BT Printed paper 14/6229) Embryos or embryos with no prospect of life also used in discussion of this topic was rejected by the Study Commission as obscuring the issue.

[232] ESchG, § 1, (1), sub-section 1.

[233] This subject is addressed in a separate section: 3.1.1.3 Problems of "therapeutic" cloning.

[234] Maximum permissible number according to § 1 (1) No. 4 ESchG.

without prior hormone stimulation; this procedure cannot, however, prevent the existence of "supernumerary" embryos but can only reduce their number. The possibility of freezing not only pronuclear stages but also egg cells offers another means of reducing the number of "supernumerary" embryos, only one egg cell being fertilised after thawing. Whether this should result in a modification of IVF techniques will not be discussed further here[235].

No precise assessment of the number of "supernumerary" embryos is possible at present. The most reliable data appears to be offered by the IVF Register. The total stock of deep-frozen embryos at the end of 2000 was 71[236]. How many of these will eventually fail to be used for further IVF treatments is unknown. The federal government was notified of 15 "supernumerary" embryos in June 2001.[237]

The number of frozen impregnated egg cells at the pronuclear stage at the beginning of 2001, according to the German ministry of health based on data from the regions, was 61,370.[238] A different number was quoted in June 2001 by the German IVF Register, at 32,123. From 1998 to 2000 a total of 126,721 pronuclear stages are reported to have been frozen throughout Germany in association with IVF.[239] However, it is not clear from the figures whether and to what extent they include "supernumerary" pronuclei, that is, those no longer required for IVF treatments.

With respect to the production of ES cells from pronuclear stages, it should be noted that this is possible only by means of creating embryos. There is also a view that the use of pronuclear stages for purposes that use up this material for the benefit of third parties would be equivalent to the production of embryos for research purposes. The pronuclear stages frozen in the course of IVF will not be taken into account here when considering the handling of embryos produced in vitro.

3.1.1.1 Problems relating to embryos produced in vitro specifically for the derivation of embryonic stem cells

The intention to produce embryos might be based on the fact either that there was a lack of other "resources" for ES cell derivation or that, for particular research purposes, ES cells from other sources would not meet the necessary quality requirements.[240]

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[235] The report of the Study Commission on pre-implantation diagnostics is to deal with the question of IVF methods.
[236] Deutsches IVF Register 2001.
[237] According to data of limited assessability from 10 federal states. (Schaich-Walch 2001).
[238] Also Schaich-Walch 2001.
[239] According to the chairman of the Board of the German IVF Register, Prof. Ricardo Felberbaum, at the scientific press conference in Bonn on 20. June 2001 (Felberbaum 2001).
[240] Lanzendorf et al. 2001. For example, the investigation of hereditary diseases would be possible with the use of ES cells with a defined genetic make-up.

The production of embryos for research purposes is prohibited in countries including Germany, Austria, Switzerland, France and Canada.[241] Between 1990 and 1998, 118 embryos were produced in Great Britain specifically for research purposes.[242] The deliberate creation of a number of embryos for the purpose of producing ES cell lines was reported from the USA for the first time in July 2001.[243]

3.1.1.2 Problems of derivation from "supernumerary" embryos

There are three possible courses of action with regard to "supernumerary" embryos[244]:

- allowing them to die by "disposal",
- carrying to term by implantation in the womb of a woman,
- use for research purposes, e.g. to create embryonic stem cell lines.

Further unlimited cryopreservation may be regarded as a fourth possibility. However, this only represents a postponement of the alternatives mentioned above.

3.1.1.2.1 Allowing embryos to die in vitro

Since the use of embryos for any purpose other than their maintenance is excluded under the Embryo Protection Act, allowing the embryo to die or cryopreservation with a view to later implantation are the only two legally acceptable options with regard to "supernumerary" embryos.

3.1.1.2.2 Use of "supernumerary" embryos for the creation of embryonic stem cell lines

3.1.1.2.2.1 Ethical assessment of the derivation of pluripotent embryonic stem cells from "supernumerary" embryos

3.1.1.2.2.1.1 Ethical assessment with regard to the material

In the case of derivation of pluripotent embryonic stem cells from "supernumerary" embryos, the act of harvesting, according to the current state of the art, is also associated with the destruction of a human embryo.

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[241] Cf. also Annex II.
[242] Department of Health 2000, P. 6. Relates to all types of research in embryos legal in Great Britain – not exclusively stem cell research.
[243] Gametes were used from pseudonymised donors who had given their informed consent for this use and were financially remunerated. From twelve women, 162 mature egg cells were harvested and fertilised with sperm from two donors. Of the 40 embryos successfully produced, three stem cell lines were developed (Lanzendorf et al. 2001, P. 135). With respect to the legal situation cf. 1.2 Legal regulations nationally/internationally and Annex II (Legal regulations in selected states).
[244] Cf. 1.2.3.1 Embryo Protection Act (ESchG).

3.1.1.2.2.1.2 Ethical assessment with respect to the origin

However, in the case of harvesting from "supernumerary" embryos the embryo has not been created for the purpose of stem cell derivation, but to give rise to a pregnancy within the relationship of a couple who cannot fulfil their wish to have a child in any other way. Since it must be assumed that, even where the number of embryos produced in vitro for this purpose is limited, it will sometimes be impossible to implant the embryos created, for reasons relating to the couple or due to other unavoidable circumstances, so that in rare cases "supernumerary" embryos will arise. Unlike the case of production of embryos for research purposes and the creation of embryos by cell nuclear transfer in the form of "therapeutic" clones, the embryo here is initially produced for its own sake and not for some other purpose to benefit a third party, so that the treatment to which the embryos concerned owe their origin is not to be regarded as an act contravening the protection of human dignity or any other worthiness of protection of the embryo.

3.1.1.2.2.1.3 Ethical assessment with respect to the high priority of the objectives

The harvesting of stem cells from "supernumerary" embryos, however, is also an offence against the protection due to each human embryo. A position that approves the harvesting of ES cells requires, by way of justification of the killing of embryos, that use for specific high-priority purposes must be the intention. Such purposes mentioned by this position are: research with a view to obtaining directly or indirectly knowledge of therapeutic benefit or at least with a view to obtaining basic knowledge, particularly concerning human individual development, especially at the molecular level and for the understanding of programming, reprogramming and transdifferentiation processes in embryonic and adult human stem cells. According to the above criteria[245], the degree of priority of these objectives may be regarded differently, these differences being assessed, in particular, according to the therapeutic relevance.

3.1.1.2.2.1.4 Ethical assessment with respect to the high priority of the means

Before an ethical decision can be taken as to whether the derivation of stem cells from "supernumerary" embryos can be regarded as *proportional* in view of the high-priority objectives mentioned, in view of the worthiness of protection due to each human embryo it must be demonstrated that such derivation is *appropriate* and *necessary* in order to achieve the objectives in question. This applies with regard both to whether such research could also be carried out in adult stem cells and also to whether it is necessary at the present time or whether ethically less controversial means should initially be selected for research for the high-priority purposes concerned.

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[245] Cf. 2.1.2 The objectives of research in human stem cells.

3.1.1.2.2.1.5 Conclusion

If it is assumed, as with the first of the positions mentioned above[246], that the moral status of the embryo in vitro is not reduced and that inviolability of dignity and protection of life are inseparable, then the derivation of stem cells from "supernumerary" embryos, which is associated with the destruction of the embryo, cannot be justified ethically even if it is carried out for the high-priority purposes in question.

If one assumes that certain limitations of the requirement to protect life do not represent a contravention of the protection of dignity due to each embryo, a balancing process appears possible in the case of "supernumerary" embryos. This applies even more to the second position mentioned above[247], which assumes a graduated worthiness of protection of the human embryo's right to life and denies protection of dignity of the embryo under basic law up to the time of nidation or altogether.

However, from the perspective of the last two views mentioned above, possible justification of the derivation of stem cells from "supernumerary" embryos, if justifiable at all, in view of the high priority attributable to the protection of life even for "supernumerary" embryos, remains bound to the strict demonstration of appropriateness, necessity and proportionality of the killing of the embryo necessarily associated with such derivation. With regard to *appropriateness*, the question of possible risks and the degree to which the objectives will be achievable must be given particular attention. With regard to *necessity*, it must be investigated, particularly by comparison with research in AS cells, whether the derivation of stem cells from "supernumerary" embryos is actually indicated, and without comparable alternatives, at the present time. With respect to *proportionality*, the way in which such derivation breaks a currently existing moral taboo must be examined, in so far as its approval justifies the use of human life for an alien purpose. This incorporates the question of the priority level of the objective[248] needed in justification of such a case.

The weight of these questions arising from ethical perspectives makes it clear that the decision concerning legal regulation could only be taken after adequate clarification of the scientific and medical circumstances involved and only after intensive public debate. These discussions should also consider the procedures and composition of the appropriate committees by which the above mentioned evidence is to be gathered and examined. This is even more the case since the dissension relating to views on the moral status of the human embryo in vitro is unlikely to be resolved within the foreseeable future.

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[246] Cf. Section "2.1.4.1 Position I: The human embryo is deserving of protection of human dignity from the beginning, i.e. from completion of fertilisation".
[247] Cf. Section "2.1.4.2 Position II: Worthiness of protection is ascribed to the human embryo in a graduated way".
[248] Cf. 2.1.2 The objectives of research in human stem cells.

3.1.1.2.2.2 Legal assessment of the derivation of pluripotent embryonic stem cells from "supernumerary" embryos

The Embryo Protection Act prohibits the use of embryos in vitro for the derivation of embryonic stem cells without exception. This applies also to "supernumerary" embryos.

These embryos were originally created for their own sake and not for an alien purpose, and therefore without violating the rights of the embryo. In this context, it must be considered whether their later use for the purposes of benefiting others is an offence against the human dignity and right to life guaranteed under basic law according to Art. 1 (1) and Art. 2 (2) sub-section 1 GG.

The question of how "supernumerary" embryos should be dealt with was already a matter of controversy before the Embryo Protection Act came into force. The passing of this Act was preceded by a comprehensive discussion including the subject of embryo research. Research in human embryos was also examined by the Benda Commission[249]. The Commission reached the majority decision that: "the creation of human embryos for research purposes is fundamentally unjustifiable. Moreover, experiments with human embryos are justifiable only insofar as they serve the purposes of identification, prevention or cure of a disease in the embryo concerned or the obtaining of defined, high-priority medical information."[250] The SPD failed in the legislative process with an application to prohibit cryopreservation in view of the subsequent problems of the creation of "supernumerary" embryos.[251] After intensive public and parliamentary debate, the legislator did not incorporate the decision of the Benda Commission. According to the ESchG, any research in embryos for a purpose other than their maintenance is prohibited

The federal and regional working group on reproductive medicine, in its final report dated August 1988[252], reached the decision to prohibit research in "supernumerary" embryos.[253]

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[249] Bundesministerium für Forschung und Technologie und Bundesministerium für Justiz 1985.

[250] Later in the report it states: "It is an open question whether sufficient basic information is yet available from animal experiments to justify approval of the need for research in human embryos at this stage. It is, however, conceivable that in the future such a need might be ethically justified." The report then names five conditions for approval in this case. Its recommendations then state: "The performance of an actual research project should be made dependent by the legislators on the prior approval by a state-authorised body which can seek an opinion or a decision on the matter, possibly from the existing Ethics Committees of the Medical Councils." Accordingly the *Draft discussion of an act to protect embryos* dated 29 April 1986 provided for the possibility of approval of such research projects by the highest federal authorities responsible, in § 2 (2) 2.

[251] Concluding recommendation and report of the legal committee, BT Printed paper 11/8057, P. 13.

[252] Federal and regional working group on reproductive medicine, 1989.

[253] The explanatory note, under section 3. Research in supernumerary embryos, stated: "A ban on all research in supernumerary embryos is justified, however, by the danger that research in such embryos could introduce a development which would not be compatible with the objective idea of human dignity. Firstly, allowing this research could lead to the creation of supernumerary embryos which would be avoidable under current circumstances in medicine. It would then be difficult to rule out such disregard of the restrictions intended to prevent the creation of supernumerary embryos. Secondly, it is feared that allowing research in supernumerary embryos could lead to a development in which the demand could no longer be covered by supernumerary

Interventions in embryonic human life are prohibited if they violate human dignity or interfere in an unacceptable way with the right to life. If one follows the arguments described in **Position I**[254] in the ethical assessment of the worthiness of protection of the embryo in vitro, the derivation of stem cells from "supernumerary" embryos is an unacceptable interference in the human dignity of the embryo and is prohibited without exception. This applies even more in the event of an offence against the right to life that is not covered by the narrow limits of the 'proviso of legality', the stipulation under the Constitution that basic rights may be restricted only pursuant to a law. In stem cell derivation, the embryo is used exclusively for the benefit of others, and its subject quality is therefore fundamentally called into question. This also applies in the case of a "doomed" embryo.[255] Balancing against other objects of legal protection is impossible with regard to human dignity.

Even "supernumerary" embryos are living creatures capable of development, and not "cadavers"[256], from which one can take certain body parts. Even the terminally ill and dying enjoy the protection of basic rights and of Art. 1 (1) and also of Art. 2 (2) GG without any limitation.[257] Cryopreserved embryos after thawing only require culture up to the blastocyst stage, and are still living during this period.

Offences against human dignity are prohibited up to the time of death of a human being.[258] The fact that the supernumerary embryo has no further chance of life is due not to its lack of ability to develop, but to the fact that the purpose of giving rise to a pregnancy in the woman whose egg cells were fertilised in vitro can no longer be achieved, for reasons associated with the woman, and that there is also no question of any other way of realising the prospect of life. If it had a mother, it could achieve birth as a human being.[259]

The representatives of **Position I/II**[260]**,** who also assume the protection of human dignity of the embryo in vitro, do not, however, regard the use of a "supernumerary" embryo for the derivation of stem cells as instrumentalisation and therefore an offence against dignity, if it is ensured that the protection of life resulting from the human dignity of each human embryo takes precedence over an equally high-ranking object of legal protection of third parties. This

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embryos alone. In this case the demand for approval of the creation of embryos for research purposes could be expected to increase in the long term..."

[254] Cf. Section "2.1.4.1 Position I: protection of human dignity is attributable to the human embryo from the beginning, i.e. from the completion of fertilisation".

[255] Sacksofsky 2001, P. 74.

[256] According to Starck 2001, P. 55.

[257] Höfling 2001, P. 217.

[258] Sacksofsky 2001, P. 74.

[259] Maintenance by means of cryopreservation is also possible over a long period, e.g. until a woman is found for embryo adoption. Cf. 3.1.1.2.3 embryo donation and adoption.

[260] Position I/II is described in section: 2.1.4.1 Position I: The human embryo is entitled to the protection of human dignity from the beginning, i.e. from the completion of fertilisation onwards.

applies only, however, insofar as the life of the embryo can still be protected and there is still a chance of its being carried to birth.

Representatives of **gradualist Position II**[261] , in balancing the basic right to life and in denying protection of human dignity for the embryo up to nidation or completely, also conclude that it is possible to permit destructive research and research for the benefit of others in "supernumerary" embryos.

In balancing values to be protected under the Constitution, in so far as this is not regarded as prohibited in view of the protection of human dignity of the embryo and the exceptional value of its right to life, the legislator must take into account, in addition to violation of the right to life, the possible threat to the right to life[262]. In practice he must take account of the fact that the right to life of large numbers of other embryos could be jeopardised if the use of "supernumerary" embryos were permitted for the derivation of stem cells. Such jeopardy could arise – many people feel –from the fact that the number of such "supernumerary" embryos could subsequently be increased deliberately. However, this would be in contravention of the current legal position, under which the existence of "supernumerary" embryos represents an undesirable secondary consequence of in-vitro fertilisation that should be avoided. However, an unwanted and unintentional increase in the number of "supernumerary" embryos is also feared. Acceptance of the possibility of balancing embryos against high-priority research interests could reduce awareness of the fact that the legislator, in the Embryo Protection Act, is clearly endeavouring to guarantee an opportunity of life for every embryo created in vitro. The decision as to when an embryo is "supernumerary", that is, when there is no longer any question of achieving further development, depends on the personal estimation of the individuals and social circumstances involved, which are not always clearly assessable. Evaluation of the actual situation – it is feared – will be difficult to separate from research interests. A demand for "supernumerary" embryos for research purposes could therefore result in a greater supply of such embryos which, according to the aims of the Embryo Protection Act should not actually be the case. A "breach of the dam" could take place that could undermine embryo protection as a whole.

The legislator must also bear in mind this danger, in the interests of respect for human life and human dignity, when addressing the question of whether the derivation of embryonic stem cells for research should be permitted.

Relaxing the ban on the performance of destructive research in human embryos would also inevitably cast suspicion on medically assisted reproduction, that it might not only be assisting couples to achieve parenthood but might also be making "material" available for scientific

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[261] Cf. Section 2.1.4.2 Position II: Worthiness of protection is ascribed to the human embryo in a graduated way.
[262] Jarass / Pieroth 2000, note 59 with further references.

purposes. The conditions for acceptance by society of the techniques of assisted reproduction would be considerably impaired. Reasons therefore emerge for not permitting the derivation of stem cells from human embryos in Germany.

3.1.1.2.3 Embryo donation and adoption

3.1.1.2.3.1 Definition of the problem

The premise for the present discussion is the assumption that the embryo is entitled to the protection of human dignity and the right to life even in vitro.

The question of whether the possibility of embryo adoption can resolve or reduce the problem of "supernumerary" embryos and also

- whether it is only discussed in theory as the third option in dealing with "supernumerary" embryos, or
- whether it has the nature of a regular case or only an exception ("emergency solution"),
- or whether it may even be a requirement under the terms of constitutional law.[263]

There are a number of problems associated with the acceptability of embryo adoption which must be defined and clarified:

- Contravention of the Embryo Protection Act?
- Parents' right of disposal?
- Effect on IVF techniques, improper "production" of "supernumerary" embryos?
- Divided motherhood?
- Psychosocial and legal consequences for the "adopted" child?
- Bureaucratic over-regulation ("waiting list places" for women willing to adopt)?
- Commercialisation?
- Necessary legal regulations (ESchG, §§1741ff. BGB, professional right for doctors)?
- Promotion of pre-implantation diagnostics ("quality-check" before adoption)?
- Overall social effects?

3.1.1.2.3.2 The concept of "adoption" in connection with "supernumerary" embryos

Neither the regulations of the German civil code on adoption (child adoption) under §§ 1741ff. BGB nor the law on arrangement of adoption (Adoptionsvermittlungsgesetz) can be applied to

[263] Höfling 2001a, P. 176 ff.

embryo adoption, since these regulations relate to the adoption of children after birth. § 1591 BGB, however, which clearly states: "The mother of a child is the woman who gave birth to it" is, however, relevant to embryo adoption. The legal principle underlying §§ 1741 BGB and the law on arrangement of adoption, protection of the well-being of the child[264], can, however, also be applied to the embryo not yet implanted, in view of its status as an independent subject in basic law[265].

3.1.1.2.3.3 Current status of discussion

Although the Benda Commission did not recommend embryo adoption, it did discuss this in a limited way as a possibility with respect to the right to life.[266] The Commission reached the following decision:

> Embryo donation is justified wherever it is used to preserve the embryo from death and a married couple is willing to adopt the child as their own.[267]

Embryo donation and embryo adoption do not constitute a punishable offence against the Embryo Protection Act.[268] This is also the view of the federal government.[269] Surrogacy is a punishable offence under the Embryo Protection Act[270], but this is not a factor in embryo donation or adoption, and provides for punishment in the event that a foreign egg cell is transferred to a woman or an egg cell is fertilised artificially for a purpose other than giving rise to a pregnancy in the woman from whom the egg cell originates.[271] The original objective of bringing about a pregnancy also exists in the case of the creation of "supernumerary" embryos and subsequent embryo adoption. The intention of the legislator with the above regulation was to prevent the occurrence of divided motherhood. The Embryo Protection Act is based on the strict connection between in-vitro fertilisation and implantation into the womb of the woman from whom the egg cell originates. The legislator did not, however, wish to take the further step of prohibiting embryo donation and adoption in general, in view of the protection of the life of the embryo which is a basic right.[272]

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[264] § 1741 BGB: "Child adoption is permissible if it benefits the well-being of the child and it is likely that a parent-child relationship will develop between the adopting parent and the child."
[265] Cf. Derleder 2001, P. 154 ff.
[266] Federal Ministry for Research and Technology and Federal Ministry of Justice 1985.
[267] Ebd., P.36.
[268] Starck 2001, P. 55; Höfling 2001a, P. 176 ff.
[269] Reply by the federal government on 7 August 2001 to the written question from Member of the Bundestag Hubert Hüppe.
[270] Cf. § 1 (1) No. 7 ESchG: "Any person .... undertaking artificial insemination or the transfer of a human embryo to a woman who is prepared to give up her child on a permanent basis to third parties after birth (surrogate mother), shall be liable to imprisonment for up to three years or a monetary fine."
[271] § 1 (1) No. 1 and 2 ESchG.
[272] In the legislative material (Federal Government draft legislation for the Embryo Protection Act, BT Printed paper 11/5460) it is stated on page 8: "The draft endeavours to combat embryo donation and the various forms of surrogacy at the early stage, by penalising artificial fertilisation with a view to later embryo transfer. The draft wishes at the same time to remove the need for a general ban on embryo donation. Such a criminal ban

Those advocating the possibility of adoption of "supernumerary" embryos point out that the unplanned orphaning of embryos gives rise to an emergency which would allow observance of the strict connection to be waived in favour of the right of the embryo to life.

Some individuals even regard embryo adoption as a requirement under constitutional law.[273] The agreement of the genetic parents is desirable here, but not a necessary prerequisite of embryo adoption and replaceable. Rights of objection by the "parents"[274] to an embryo adoption cannot be justified under the constitution.[275] However, the questions of individual right of family and personal status are still to be regulated by the legislator. Others consider the informed consent of the "parents" to embryo donation as indispensable.[276]

Wide-ranging objections have, however, also been raised to embryo adoption. If it is assumed from the Embryo Protection Act that the creation of embryos in vitro is legitimate only in order to treat the infertility of the couple concerned, in the event of "supernumerary" embryos the death of these embryos – as with embryos implanted but not leading to a pregnancy – must be accepted. Transfer to another woman would, from this viewpoint, contravene the limitation to the treatment of infertility imposed on in-vitro fertilisation by the Embryo Protection Act, in agreement with Basic Law, and would result in divided parenthood with its negative effects on the well-being of the child. Reference is also made to ethically highly problematic possible consequences such as (covert) surrogacy, commercialisation and forced adoption.[277]

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would not be without concerns, at least in cases in which embryo donation offers the only possibility of preserving the embryo from death."

[273] Cf. Röger 1999, P. 117 and Höfling, 2001a, P. 176 f.: If "pre-implantation parents", for whatever reason, are no longer interested in an implantation, the State is obliged to make available an alternative allowing the survival of the embryo. The cryopreservation of "supernumerary" embryos which, as indicated in § 9 No. 3 ESchG, is not prohibited in itself, is however a dilatory solution. In addition, the possibility of pre-implantation adoption is to be examined.

[274] The term is placed in inverted commas here because adequate terminology has not yet been developed in common parlance for situations arising in in-vitro reproductive medicine as distinct from the conventional meanings.

[275] Höfling, 2001a. P. 179 f. Unlike the proposal of the Benda Commission (cf. Federal Ministry of Research and Technology and Federal Ministry of Justice 1985), that wished to give precedence to the rights of determination of the potential parents concerning their genotype over the obligation to maintain life. The objection made by Coester-Waltjen in the expert report to the 56th German law congress in 1986 was: "Following the birth of a child, the parents have no right to end the life of the child in the event that a child with their genetic characteristics chooses a path which is contrary to their ideas. Here too the law demands the rights of the genetic parents to tolerate if necessary a division of the physical and legal parent-child relationship by adoption. ....it is not clear why the protection of unborn life should be less important here; the prenatal situation gives rise to no special features that would make the birth of the child (by others) unreasonable for the physical parents. In the interests of the child, being born, as opposed to destruction, is the better alternative."

[276] Müller-Terpitz 2001, P. 283: "for reasons of protection of the personality, one should not fail, however, to make such an adoption dependent on the consent of the genetic parents or of the surviving parent."

[277] In the guidelines of the scientific advisory board of the Federal Medical Council on the performance of assisted reproduction, status 3 December 1998, reference is made to the possible effects of divided motherhood on the child. The entire physical and intellectual development of the child would be significantly affected by the hereditary characteristics originating from the genetic mother and also by the close relationship existing during pregnancy between the child and the mother carrying the pregnancy to term.

A further point against allowing embryo adoption is that there could be cases in which, after creating the embryo, the mother is not in a position for health reasons (e.g. due to a malignant disease of recent onset) to carry the embryo – although she still wishes to have children. In such a case, parents would regard themselves as obliged to opt for embryo adoption as the only chance of survival, from the conviction that the embryo has the right to life on the one hand and the fact that surrogacy is legally prohibited (in Germany) on the other. Such parents – and probably also the resulting children – will resist the tearing apart of their families based on a legal regulation (prohibition of surrogacy alongside toleration of divided motherhood).

3.1.1.2.3.4 Considerations for and against

All deliberations on the desirability and permissibility of embryo donation and adoption must be based on the intention of the Embryo Protection Act, according to which in-vitro fertilisation should not result in the creation of "supernumerary" embryos. This is intended not only to protect the embryo but also to protect the woman with regard to deeply invasive ovarian stimulation treatment and the avoidance of multiple pregnancies.

Based on the position that the embryo in vitro deserves protection of its basic rights, in particular the right to life, deliberations on the possibility of an embryo donation or adoption may broaden the debate concerning the alternatives of disposal or use for research purposes and prevent automatism in the sense of a "research imperative".

Embryo adoption offers the prospect of life to "supernumerary" embryos. If embryo adoption is approved as a basic possibility for dealing with "supernumerary" embryos, it must be considered whether embryo adoption should be permitted as a regular occurrence, only in exceptional cases or simply as a last resort.

The position according to which the State is obliged "to offer alternatives allowing survival of the embryo" (cryopreservation, adoption), appears to be a peremptory position.[278] It would mean that in every case a woman would have to be found who would be prepared to act as the mother. This would come close to a "social obligation" on women to reproduce and for this reason does not seem acceptable. Embryo donation and adoption is therefore suggested even by its advocates primarily only in exceptional circumstances as a solution of last resort[279].

An essential aspect in considering embryo donation and adoption is the attempt to solve the problem of "supernumerary" embryos and to allow a chance of life as a last resort to "orphaned" embryos. This can by no means be regarded as a normal case or as an obligatory solution. The extent to which this would benefit the child is also problematic. Since this emergency solution cannot entirely avoid the existence of "supernumerary" embryos, it is to be

[278] Höfling 2001a, P. 176 ff.
[279] Starck, 2001, P. 55; Wuermeling 2001, P. 48.

regarded only as a partial solution to the problem of "supernumerary" embryos. The choice between allowing the embryo to die or releasing it for research therefore remains in individual cases.

3.1.1.2.3.5 Conclusion

Embryo adoption could in any case be regarded as a possibility for providing "supernumerary" embryos with a chance of survival in the last resort as an alternative to disposal. It may be, however, that this represents only a partial solution to the problem of "supernumerary" embryos.

On the other hand, an objection to embryo adoption is that it could be associated with divided motherhood, the risk of covert surrogacy and of affecting IVF techniques, the risk of inducement to create "supernumerary embryos" and of commercialisation.

An important outcome of the debate on embryo adoption must be the demand that all methods leading deliberately or with tacit approval to "supernumerary" embryos, should be strictly rejected and prohibited.

3.1.1.3 Problems of "therapeutic" cloning

Cloning is a method for the production of genetically identical duplicates of carriers of genetic information, of individual cells or complete organisms. In humans, identical twins, having the same genetic make-up, can occur naturally.[280]

The term "therapeutic" cloning describes the cell nuclear transfer of a somatic cell (body cell) into an enucleated egg cell for the purpose of developing a totipotent cell or an embryo up to the blastocyst stage, in order to derive embryonic stem cells for research purposes and in the long term for cell, tissue or organ replacement. In animal experiments, this has been carried out both with cells of the same species and also with egg cells of other animal species. The first mammal produced by the cloning method was "Dolly the sheep”. Experiments have also been reported in which cell nuclei from human somatic cells have been transferred into enucleated egg cells from cows and rabbits.[281]

The method of "therapeutic" cloning differs from reproductive cloning[282] not in its technique, but with regard to its intention: in reproductive cloning, genetically identical offspring

[280] The artificial contrivance of this procedure in vitro, embryo splitting, is prohibited under § 6 ESchG.
[281] Cf. 1.1.1.2.1 Derivation and: "Versuchkaninchen Mensch” (The human guinea-pig) 2001, and: "China finances the crossing of human cells with those of animals." 2001.
[282] Reproductive cloning is unanimously rejected internationally, but has only been banned by law in a few countries and is not prohibited under international law. This, however, does not exclude the pursuance of this objective by individual researchers as demonstrated by reports from the gynaecologist Severino

("delayed identical twins") are created. The technique of "therapeutic cloning" is at the stage of basic research. Therapeutic applications cannot be expected within the foreseeable future. Apart from applications in humans, the technique of cloning by cell nuclear transfer is also being developed for animal breeding.

The totipotent cells created by this technique, unlike embryos from natural fertilisation (of egg and stem cell) are genetically related to only one "contributing parent", the donor of the cell nucleus. The genome of the embryo is almost completely known from the outset.[283] It is hoped that the genetic identity of the embryo with the cell nuclear donor will allow the production of immunologically compatible biological material which will not be rejected in the body of the donor of the cell nucleus.[284]

Experience from the successful cloning of animals shows that a large number of experiments are necessary to obtain a living creature capable of survival.[285] It is therefore assumed that even with "therapeutic" cloning, a large number of cell nuclear transfers must be carried out in order to obtain a cloned ES cell line and to minimise genetic and epigenetic defects in the ES cell lines produced.

3.1.1.3.1 Legal situation

Cloning from embryos, fetuses and humans and also from cadavers is prohibited by the Embryo Protection Act.[286] However, doubts are expressed as to whether prohibition of the offence of "therapeutic" cloning is sufficiently unequivocal. Legal clarification is urgently required here.[287]

3.1.1.3.2 Legal questions on egg cell donation

"Therapeutic" cloning requires the availability of female egg cells for nuclear transfer. The Embryo Protection Act prohibits egg cell donation for reproductive purposes.[288] The intention

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Antinori/Panayiotis Zavos (*Scientists want to clone humans*. 2001) and Brigitte Boisselier of the Raelian Sect (Boisselier 2001).

[283] Genetic differences between various clones from cell material from the same donor may arise as a result of new mutations. The mitochondrial 13 genes contained in the cytoplasm of the enucleated egg cell give 99.98 to 99.99% genetic identity unless the egg cell and egg nucleus originate from the same woman (cf. Oduncu 2001).

[284] Cf. 1.1.3.2.2 Cell and tissue replacement from cell nuclear transfer (autologous method).

[285] Cf. 1.1.1.2.1 derivation.

[286] § 6 ESchG.

[287] Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and further developments emerging, BT Printed paper 13/11263, particularly section D.

[288] § 1 (1) No. 1 and 2 ESchG. The current prohibition of (heterologous) egg cell donation in the context of reproductive medicine does not contravene Art. 3 (2) GG, although sperm donation is treated differently by the legislator. On the other hand, no obligation can be derived on the basis of the constitution to prohibit egg cell donation – except to allow the woman's own pregnancy – although the legislator has opportunities for far-reaching limitations, cf. Höfling 2001, P. 7.

of the legislator was to prevent divided motherhood in the interests of the child's well-being. Egg cell donation for research purposes is not forbidden by the Embryo Protection Act.[289] This also includes the pursuance of a potentially therapeutically effective objective, which was not yet known in 1990. The extent to which egg cell donation for non-reproductive purposes is permissible is therefore determined in accordance with general criminal, civil and medicolegal principles. Egg cell donation is an invasive intervention for the benefit of others, associated with a considerable risk of damage to health for the woman.[290] The regulations allow interventions in humans for the benefit of others– as with medical experiments in humans or with organ donation from the living –only under limited circumstances even where consent has been given.[291] A decisive factor in assessment of acceptability is the proportionality of the procedure. In spite of the existence of consent given after detailed information has been provided by a doctor, the physical intervention for the benefit of others remains contrary to law[292], if the burden imposed by the procedure is disproportionate as regards the purpose of the intervention.

3.1.1.3.3 Ethical assessment of the derivation of pluripotent embryonic stem cells by "therapeutic" cloning

3.1.1.3.3.1 Ethical assessment with respect to the item

Under the criterion (also laid down by the Embryo Protection Act) that a human being is present if a cell has the actual potential itself to develop into a human being, the cell created by transfer of a somatic cell nucleus into an enucleated egg cell – like the embryo produced in vitro from egg and sperm cell – must also be regarded as a human embryo to which the corresponding worthiness of protection is due. Since the moral status of the embryo is linked to the criterion of being a human being, the intention to create such a cell exclusively for the derivation of autologous stem cells does not allow these cells – it is argued – to become part of a "natural biography", though this intention cannot abolish the status associated with existence as a human being. The consideration that the same cell on implantation (reproductive cloning) could develop into a mature human being suggests the acceptance of such a status.

3.1.1.3.3.2 Ethical assessment with respect to origin

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[289] See official justification of the draft legislation from the Embryo Protection Act, BT Printed paper 11/5460 dated 25 October 1989, P. 8: "transplantations in which there is no intention of fertilising the transferred egg cell are excluded from liability to punishment."
[290] Cf. Pichlhofer / Gross / Henke 2000, P. 11 ff.
[291] Pichlhofer / Gross / Henke 2000, P. 41 f. with further references.
[292] Resulting in punishment for physical injury in accordance with § 228 StGB.

If this deliberation is correct, an embryo created by cell nuclear transfer represents a living human being whose creation differs in an ethically significant manner from that of other human beings, insofar as it is created, in the case of "therapeutic" cloning deliberately as the delayed twin of the cell nuclear donor from which the required almost autologous stem cells are to be harvested at the blastocyst stage. This "therapeutically" cloned embryo is to be killed in this process. Therefore, all the comments concerning protection of human dignity and life made above with regard to "supernumerary" embryos also apply for the embryo created by cell nuclear transfer. In the case of reproductive cloning, the individual concerned has to bear the consequences of this objective set by third parties permanently and in a way not otherwise encountered. Even if his genome is not completely identical with the genome of the cell nucleus donor because of the modified mitochondrial components, there is likely to be a large degree of concordance with a genome already existing in its phenotypic expression. Therefore, in the case of reproductive cloning, the embryo created is likely to be deprived by the intentional decision of third parties of the natural conditions unique to every human embryo created in the natural way, having a father and mother, that is, being a living creature which is "random" in its make-up from the two haploid sets of chromosomes of the parents and unpredictable in detail with regard to its phenotypic characteristics.[293]

3.1.1.3.3.3 Ethical assessment with respect to the objectives

Without doubt, the derivation of transplantable autologous tissue by means of the cell nuclear transfer technique described, is a high-priority therapeutic objective, if it is capable of preventing the rejection reactions otherwise to be expected. However, this objective cannot remove the ethical objection mentioned, particularly if the harvesting of transplantable tissue from AS cells – to the extent that this is possible – can lead to the same objective.

The aim of research to be performed in stem cells from embryos created by "therapeutic" cloning is regarded as being of high priority in so far as it concerns the understanding of the programming, reprogramming and transdifferentiation processes in embryonic and adult human stem cells. However, even this priority objective – even if definitely feasible and required by this means only for a limited period – cannot abolish the ethical concerns mentioned.

This is true particularly in view of the fact that the same technique as that used for "therapeutic" cloning can also be used for reproductive cloning and an embryo created for the

[293] Not a few critics regard this as a contravention of basic requirements of social ethics such as equality and the prohibition of discrimination. According to R. Dworkin (Dworkin 1999, P. 39) we are dealing here with process that intervenes deeply in the connection between nature and nurture that is constitutive for the human make-up. J. Habermas regards reproductive cloning as an intervention in the natural ‘Selbstsein” (literally, self-being), resulting in asymmetry of the conditions of recognition that constitute the moral subject and therefore affects generic ethics (Habermas 2001).

first purpose can at any time be used for the second purpose. Therefore, the arguments that have led reproductive cloning to be rejected worldwide also apply to "therapeutic" cloning.

3.1.1.3.3.4 Ethical assessment with respect to means

A further point against the ethical acceptability of stem cell derivation by cell nuclear transfer is also the means required in this connection. In particular, the large number of egg cell donations required for successful use of the technique must be regarded as unacceptable. Not only does this represent an unreasonable burden for the woman concerned, but must also have worrying effects on the self respect and social image of women, if they are seen in this way as "suppliers of raw materials".

If the method of creating an embryo by cell nuclear transfer, undertaken exclusively for the derivation of stem cells, is regarded as affected by all the arguments against reproductive cloning, all the risks and side effects observed during reproductive cloning in animals must be mentioned, which make transfer of this technique to humans appear currently unjustifiable, quite apart from the other ethical problems mentioned and also apart from the question as to whether cell nuclear transfer is feasible at all in human beings.

3.1.1.3.3.5 Conclusion

If it is assumed that even in vitro the moral status of the human embryo is not graduated and that it is therefore entitled to protection of dignity and life, and if the derivation of stem cells by "therapeutic" cloning represents not only a violation of protection of life but also of dignity, human life is being created here solely to be destroyed for the promotion of other human life. Even the undoubtedly high-priority objective cannot change these circumstances.

If one assumes that the worthiness of protection of the human embryo is graduated, rejection is less severe. In this case, however, the justification of proportionality is linked to strict demonstration of the appropriateness and necessity of the procedure used. The question of whether the justification relates only to a limited research phase or to broad use of the technique for treatment also plays a role. Even assuming a graduated increase in the protection of the human embryo, the problem of egg donation and the associated negative side effects would have to be given special weight.

Irrespective of the varying assessment of the moral status of the human embryo, the ethical legitimacy of "therapeutic" cloning is also countered by the arguments that suggest that reproductive cloning is a contravention of human dignity and the associated requirement of equality. To the extent to which the technique of cell nuclear transfer can be used and misused for reproduction of a human being, these arguments must also impact on "therapeutic" cloning.

3.1.1.3.4 Legal assessment of the derivation of pluripotent embryonic stem cells by "therapeutic" cloning

The question is whether the embryo created by "therapeutic" cloning enjoys the same status under the constitution as the embryo produced by fusion of the egg and sperm cell in vitro. This is almost unanimously agreed.[294] The protection of unborn human life is based primarily on the recognition that this is a continuous development from the fertilised egg cell through the embryo to the human being at birth. The decisive factor is that an embryo develops as a living human being, and whether or not it has actually reached the stage of independent viability or birth is immaterial.[295]

This is occasionally disputed, with the statement that the embryo created by "therapeutic" cloning is an artificially assembled totipotent cell that does not represent an embryo in the sense of early human existence. Unlike the embryo arising from sexual reproduction (by fertilisation of the egg cell by a sperm cell) this totipotent cell has no parents, at least prior to nidation. The human being from which the cell nucleus originates is neither father nor mother, but the identical twin of the totipotent cell. This totipotent cell is therefore not an embryo in the sense of the Embryo Protection Act, which is regarded as connected with sexual reproduction.[296] As to whether such an assembled totipotent cell may be created and what protection it enjoys under basic law, relates not to the violation of human dignity but only to the threat to human dignity, because the use of such a cell for the purpose of reproduction would deliberately bring to life a human being with no fixed place within a biographic order. In principle, therefore, the creation of such an artificial cell with totipotency, produced with destruction of the connection with reproduction, must be prohibited by the legislator. Whether there might be extraordinary grounds that would permit an exception would have to be discussed. In the final analysis, this view may represent an exception to the prohibition.

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[294] Sacksofsky 2001, P. 77.
[295] Höfling 2001a, P. 216.
[296] This conclusion is contrary to the wording of § 6 ESchG, in which (prohibited) cloning is defined as any person "artificially causing a human embryo to be created with the same genetic information as another embryo, a fetus, a human being or a cadaver". In practice there is also a broad consensus that "therapeutic" cloning is prohibited, cf. also Deutsche Forschungsgemeinschaft 2001b, P. 22 and Report on the possible need for legislative action with regard to the Embryo Protection Act in view of the techniques used in the cloning of animals and further developments emerging (Report on Cloning), BT Printed paper 13/11263 and the Embryo Protection Act (cf. 1.2.3.1 Embryo Protection Act (ESchG)), although clarification of the law is regarded as necessary.

3.1.2 Research in imported ES cells

3.1.2.1 Legal situation in respect to research and imported ES cells

The legal permissibility of research in ES cells is based on the classification of ES cell material as pluripotent.[297]

Importation from another country in which the derivation of embryonic stem cells is not a criminal offence is the only legally permissible way of procuring pluripotent embryonic stem cells in Germany. The prerequisite is that there should be no connection between the ordering or requisitioning of the embryonic stem cells and their production from embryos. Otherwise this would constitute criminal participation in the use of embryos for a purpose not contributing to their maintenance which is punishable under German law.[298] The import of such stem cells, that were already in existence at the time of entering upon the contractual agreement concerning the passing on of stem cells already in existence as cultures, the creation of which is fully documented and demonstrable with regard to circumstances and time, is therefore not a criminal offence.

Other laws or official regulations limiting the importation of pluripotent human embryonic stem cells do not currently exist in Germany. There are also no regulations at EU level that limit the importation into the EU or from other EU states into Germany. Nor are any state export restrictions known on the part of possible exporting states outside the EU, such as Israel, the USA and Australia. However, often far-reaching restrictions do exist under the law of contract and patent law.[299]

3.1.2.2 Ethical assessment of research in embryonic stem cells

3.1.2.2.1 Moral views held within society

The possibility that research in embryonic stem cells may be carried out in Germany by importing pluripotent stem cells from other countries, has raised feelings of alienation and

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[297] Cf. 1.1.1.1.1 Derivation and 1.1.1.6 Totipotency/pluripotency. Should suggestions that ES cells might be totipotent be confirmed scientifically, ES cells would have to be classified as embryos under existing law.
[298] Cf. 1.2.3.1 Embryo Protection Act (ESchG).
[299] In the USA the transfer of biological material at home and abroad is regulated by far-reaching standardised agreements (Material Transfer Agreements). Application for a special export licence is necessary only in exceptional cases, e.g. for materials that can be used in biological weapons or for biological samples from protected species of animals. Material Transfer Agreements usually contain regulations concerning the contractual and patent rights of ownership and disposal to the material and subsequent material and to the findings of research with the material, restrictions on the authority to use the material for scientific purposes and the obligation of the recipient to notify the issuer of possible commercial opportunities for utilisation, and, prior to such utilisation, to conclude with the issuer a special utilisation contract with corresponding financial obligations.

rejection in some sections of society. The attempt to uphold a ban on the derivation of such cells without renouncing the fruits of research in these cells is clearly regarded not only as a legal contradiction in values but also as an ethically dubious case of "double standards". Others also regard the legal permissibility of importation as an ethical legitimisation of the ethically unacceptable derivation of ES cells and therefore also reject research in imported ES cells. The underlying ethical feeling here in both cases is that no discrepancy should exist between the awareness of standards and the regulation of actions, and that exploitation of the options existing in law cannot be divorced from the question of ethical justification. There can be no disputing this underlying intuitive realisation, but it requires distinctions to be drawn with regard to ethical evaluation of the potential importation permitted by law.

3.1.2.2.2 Ethical assessment with respect to the material

To the extent that the stem cell lines to be imported for research purposes, as described above, are pluripotent[300]and are therefore not embryos, the ethical problems relate not to the *material object* of the research made possible by such imports.

3.1.2.2.3 Ethical assessment with respect to the origin

The ethical problem lies rather with the derivation of these stem cell lines from embryos, in so far as these cell lines were produced from embryos created for that specific purpose, from embryos produced by cell nuclear transfer ("therapeutic" clones) or from "supernumerary" embryos.

The weight of the ethical objections raised to importation of such stem cell lines depends on the ethical assessment of these methods of derivation. Importation of stem cell lines from embryos created purposely or derived from cell nuclear transfer would be possible without ethical objection only from the perspective of a position that regarded the worthiness of protection of the embryo in vitro as non-existent, or clearly reduced.

If one assumes that worthiness of protection is not reduced and that the use of "supernumerary" embryos constitutes a violation of human dignity and therefore that such use cannot be considered even for high-priority objectives, correspondingly strict reservations apply to the importation of stem cell lines from "supernumerary" embryos. If the view is held that the use of "supernumerary" embryos is not a violation of human dignity as such and that intervention in the right to life of these embryos is potentially justified under certain conditions in view of other priority objectives, then a similar assessment also applies to the importation of stem cell lines derived by this method in other countries. The same applies to the position based on a diminished worthiness of protection for the embryo.

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[300] Cf. 1.1.1.1.1 Derivation and 1.1.1.6 Totipotency / Pluripotency

Even for the position that regards the harvesting of stem cells from "supernumerary" embryos as ethically unjustifiable, some differentiation is necessary between the method of derivation and the act of using the stem cell lines, with regard to the weight of the ethical problem. Also of importance is the question of whether such use relates to existing stem cell lines or whether it gives rise to the derivation of additional stem cell lines and therefore to the destruction of further "supernumerary" embryos.

3.1.2.2.4 Ethical assessment with respect to objectives

If the balancing of the right to life for "supernumerary" embryos with other objectives and values is regarded as ethically justifiable, these must be of particularly high priority.

Possible high priorities might be: the gaining of directly therapeutically useful information, the gaining of indirectly therapeutically useful information and the gaining of basic knowledge, in particular concerning development of the human individual, especially at molecular level and to the understanding of the programming, reprogramming and transdifferentiation processes in embryonic and adult human stem cells.

The level of priority of these objectives may vary in kind, in accordance with the criteria mentioned above[301] therapeutic relevance being the decisive factor.

3.1.2.2.5 Ethical assessment with respect to the means used

If an ethical balancing process of the kind described is held to be legitimate, the above criterion[302] applies analogously for the importation of human embryonic stem cell lines, that ethically less controversial methods are preferable to the more controversial and that the lack of alternatives to the controversial means must be established before entering upon the process of weighing ethical considerations with regard to priority objectives.

3.1.2.2.6 Conclusions

Unanimously regarded as not ethically legitimate is the importation of embryonic human stem cell lines derived from *stem cells produced specifically for that purpose or created by cell nuclear transfer*. Since the method of derivation, from the standpoint of undiminished protection of human embryos, must be seen as a violation of human dignity and even from the standpoint of reduced protection as a mode of action that contravenes the worthiness of the embryo to be protected, the importation of stem cell lines derived by such a method must also

[301] Cf. 2.1.2 The objectives of research in human stem cells
[302] Cf. 2.1.2.2 for evaluation of these objectives

be regarded as ethically dubious, particularly since the appropriateness of and need for these methods of derivation are dubious, for the reasons stated[303].

With respect to the importation of stem cells derived from "supernumerary" embryos, approval *without limitation* is ethically justifiable only if the derivation of stem cells *from "supernumerary" embryos* for priority purposes is also accepted in principle. Those who hold this view, if they are to be consistent, must consider a change in the legislation.

If the derivation of stem cells *from "supernumerary" embryos* is regarded as justifiable, however, on the basis of a balancing process roughly in accordance with the above criteria, the importation of stem cell lines obtained from these can only be approved if it is appropriate and necessary *in specific individual cases* in order to attain objectives of a priority that makes the importation appear to be proportionate. This applies in particular where importation is for research needed only as an intermediate stage, intended to obviate the need to derive such cells from human embryos in future, and where it is limited exclusively to stem cell lines already in existence.

If all derivation of stem cells from "supernumerary" embryos is regarded as ethically unjustifiable since it violates human dignity, approval of the importation of such stem cell lines is also a contradiction in ethical values. However, from this standpoint, the question arises as to how the existing legal situation is to be handled. If in fact it is assumed that there is not to be a general legal prohibition, from the standpoint described above it would be appropriate to consider linking the current legal permissibility of importation to specific individual cases and strictly defined licensing conditions, as the lesser evil. This does not alter the fact that, from this standpoint, the legality of research in imported embryonic stem cell lines does not absolve the individual researcher of ethical responsibility.

Criteria such as promoting Germany as a research location and the consideration of economic aims must be regarded as clearly of secondary importance to the above criteria such as the worthiness of the human embryo to be protected on the one hand and the priority objectives of treatment and research on the other.

3.1.2.3 Concern relating to the existing legal situation

The view is expressed that this legal situation with regard to importation contravenes the spirit of the Embryo Protection Act. It is felt that the Embryo Protection Act contains no relevant regulation only because the problem was not foreseeable at the time of creation of the Act, and that the Embryo Protection Act must therefore be amended accordingly.

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[303] Cf. 3.1.1.1 Problems of embryos created in vitro specifically for the derivation of embryonic stem cells.

Against this, the objection is raised that criminal law can only regulate the ethical minimum, so that the provisions of the Embryo Protection Act are rightly limited to the protection of high-ranking objects of legal protection such as embryos and that, in any case, participation in the killing of embryos available abroad and their use for a purpose other than their maintenance is prohibited by the Embryo Protection Act in association with general criminal law.

The objection to this is that a ban relating only to participation in offences abroad is inadequate. The (legally permitted) demand for stem cell lines already cultured abroad could result in the production of new stem cell lines and therefore in the destruction of increasing numbers of embryos. Legal toleration of importation and research in the imported stem cells would therefore constitute toleration of the method of derivation and the destruction of embryos. The moral feelings in the population relate equally to the legal aspect. There is a widespread awareness of the need for identity of law and ethics. If law and ethics diverge, this would lead to an attenuation of the legitimacy of the law. Particularly following the intensive debate on the scope of the constitutional norms of Art. 1 and 2 (2) GG in relation to the embryo in vitro, new legal regulations are required that bring the import regulations into line with the Embryo Protection Act.

3.1.2.4 Possibilities for resolving the contradiction between the ethical assessment on the one hand and the legal situation in Germany on the other

3.1.2.4.1 Prohibition of importation of ES cells

Research in imported embryonic stem cells is covered by the freedom of research guaranteed under German Basic Law[304]. Article 5 (3) of Basic Law (GG)[305] is not subject to limitation or qualification by statute; the basic right is guaranteed without reservation. But even basic rights guaranteed without reservation are subject to limitations in their implementation, though such limitations must arise directly from the constitution itself. The deciding formula of the Federal Constitutional Court states: Only competing basic rights of third parties and other legal rights given priority under the constitution are in a position, bearing in mind the unity of the Constitution and the entire order of rights protected by it, to restrict even unlimited basic rights in individual circumstances.[306] In the balancing process, freedom of science would not be given absolute priority over values conflicting with it and also protected by Constitutional law.[307] The constitutional legal principle of proportionality must also be observed. For the balancing process, a grading system is then proposed according to how far the scientific activity remains within the individual personal "purely academic" sphere of knowledge or, with propagation of

[304] This applies provided that the ES cell lines are pluripotent cells. Cf. 1.1.1.6 Totipotency/Pluripotency.
[305] Art. 5 (3) sub-section 1 GG: "Art and science, research and teaching are free."
[306] Cf. Dreier 1996d, note 88 f.
[307] Dreier 1996d, note 89.

its findings, will also enter "the outside world of State and society", or whether it constitutes basic theoretical or applied research.[308]

In the matter of prohibition of the use of embryos for a purpose not directly contributing to their maintenance and in the prohibition of cloning[309], if it is clearly a question of the rights of third parties (the protection of incipient life under Art. 2 (2) or Art. 1 of Basic Law[310]) conflicting with Art. 5 (3), then, in the case of the importation of already established pluripotent embryonic stem cells, no basic rights conflict directly with the basic right in Art. 5 (3) GG, since the decision relating to the life and death of the embryo has already been taken here prior to importation and a human individual cannot develop from pluripotent stem cells[311]. Pluripotent stem cells do not enjoy the status to which basic rights are ascribed.

Other legal values of constitutional importance in terms of the jurisdiction of the German Constitutional Court[312] may include the fundamental value judgement of the constitution in favour of life and human dignity. This value judgement may be affected by the approval of importation, because many take the view that the use of stem cells also condones the method of their derivation. It is further feared that human dignity and the right to life, as protected by the constitution, could be jeopardised directly if importation should lead to a demand for the production of new stem cell lines. These basic rights regulations would be affected by the production of new stem cell lines. Examination of such obvious risks is part of an assessment of consequences that the legislator is obliged to undertake on the basis of the State duty of protection arising from Articles 1 and 2 of Basic Law[313]. The fact that legal restrictions are possible even before conflicts actually occur between freedom of research and other basic rights is evident, not least from the legal restrictions imposed by the Animal Protection Act on animal experiments needed for research, in particular § 7 (3) of the Animal Protection Act, which allows experiments involving vertebrates only if they are ethically justifiable.[314]

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[308] Dreier 1996c, note 33.
[309] §§ 2 and 6 ESchG
[310] Cf. 2.1.6 The question of assessment of the moral status of the human embryo under the terms of Basic Law (GG)
[311] Cf. Current situation 1.1.1.1.1 Derivation and 1.1.1.6 Totipotency / Pluripotency.
[312] Other objects of protection by law recognised by the German Constitutional Court include: the setting up and functional capability of the German armed forces, functional administration of (criminal) justice, health care or unspecified common values protected by constitutional law. Cf. Dreier 1996d, note 88.
[313] Impairment of the basic right to life exists not only in injury to life and health, but possibly also in a threat to these, cf. Jarass/Pieroth, 2000, Art. 2 note 59. The German Constitutional Court justified the permissibility of imposing a ban on organ removal from living persons in terms of the direct threat to the basic rights of third parties, in this case protection of life, also referring to the need to be aware of international developments such as possible transplantation tourism". Cf. parliamentary decision BVerG 1 BvR 2181/98, Neue juristische Wochenschrift 1999, 3399 ff.
[314] Cf. BVerfGE 49, p. 132.

The extent to which a general ban on the importation of human embryonic stem cells would be compatible with European law is also unclear. Introduction of a ruling on importation agreed within the EU and valid throughout the EU is under discussion.[315]

In this context, the degree to which a general import ban could be regulated by law is difficult to decide. A definitive estimation by the Study Commission of the leeway available under constitutional law is therefore impossible. The legislator is the primary interpreter of the constitution and has to determine by law the boundaries that can and should be drawn under constitutional law. The deliberations of the Study Commission therefore concentrate on the ethical questions on which the legislator's assessment is also based.

3.1.2.4.2 General approval of the importation of ES cells

This position within the range of opinions is adopted only by advocates of that view of the status of the embryo described in the section of the Interim Report concerning the moral status of the embryo as the "radical gradualist position"[316].

3.1.2.4.3 Limitation of importation

As an alternative to the prohibition of importation, the permissibility of importation may be made subject to strict conditions. These conditions may link the permissibility of importation to certain criteria, e.g. allowing the importation of ES cells only where it is demonstrated that their use in the individual case in question is appropriate, necessary and proportionate. Conditions for the importation of ES cells can also be linked to the origin and circumstances of derivation of the embryonic stem cells. It would be possible, for example, to restrict importation to those stem cell lines derived from cryopreserved "supernumerary" and permanently orphaned embryos, with further additional conditions being satisfied regarding their derivation. These conditions relate, amongst other things, to the voluntary consent of the donor couple, given after being informed of the nature and purpose of the research and its potential commercial exploitation (qualified informed consent), and the assurance that commercial interests were excluded, both on the part of the doctors and researchers involved and also on the part of the donor couple, in the derivation process and in the declaration of consent.

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[315] The protection of animals is not currently established in the Constitution and is still the subject of constitutional political deliberation. However, the German Constitutional Court speaks of the concept of an ethically orientated protection of animals in the sense of shared responsibility of humans for living creatures under its care. This brings into play the image of human beings under Basic Law that represents the constitutional reference point for animal protection. The legislator is entitled to enforce this human responsibility by means of basic rights limitations, cf. Starck 1999, note 383 with further references.

[316] Cf. section "2.1.4.2 Position II: Worthiness of protection is ascribed to the human embryo in a graduated way".

In principle, the same questions arise here with regard to restriction of the freedom of research as to the general ban on imports.[317] The legislator must decide to what extent the permissibility of research in imported stem cells in favour of other constitutional values must be linked to certain preconditions for approval.

The strictest regulation and nearest to a general ban on importation would be that proposed by some individuals, permitting the importation only of those embryonic stem cell lines established, in accordance with the decision of the US President, prior to 9.00 p.m. EDT[318] on 9 August 2001, the date of this decision, and included in a register drawn up by the NIH[319].

Regulation of importation along these lines would have to be put in place by the introduction of a legal requirement for import approval, such approval being conditional on the fulfilment of the legal preconditions.

In principle, the same questions arise here in relation to the limitation of freedom of research as arise with respect to a general import ban. The legislator must decide to what extent the permissibility of research in imported embryonic stem cells in favour of other constitutional values is to be linked to specific preconditions for approval.

3.2 Regulatory options and recommendations

3.2.1 Regulatory options and recommendations for the derivation and use of embryonic stem cells from “supernumerary” embryos

The derivation of embryonic stem cells requires the "destructive use" i.e. the killing, of embryos.

The Embryo Protection Act prohibits by law

- the creation of embryos for a purpose other than to give rise to a pregnancy (§1 (1) sub-section 1 ESchG) and therefore the creation of embryos for the purposes of stem cell derivation and
- in general, use for the benefit of others of the embryo created in vitro (§2 (1) ESchG), and therefore also the use of "supernumerary" embryos for the derivation of stem cells.

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[317] Import regulations limited to the observance of certain procedural regulations (notification, documentation and reporting obligations etc.) do not represent a prohibited interference in the freedom of research. The same applies for guidelines, compliance with which is made a condition of public funding.

[318] EDT: Eastern Daylight Saving Time.

[319] National Institutes of Health 2001b: The cell lines must satisfy the following criteria if they are to be used in research involving US public funds:

- derivation of the cells was initiated before 9 August 2001,
- informed consent has been obtained from the couple from whom the embryo originated,
- the cells are derived from an embryo created for reproductive purposes but which can no longer be used for that purpose (known as a “supernumerary” embryo),
- there was no financial inducement to make the embryo available for research.

From the ethical viewpoint, the following positions are held:

- from the viewpoint of those that recognise human dignity and the right to life for the human embryo from the beginning, the creation and use of an embryo for a purpose other than its maintenance represents instrumentalisation contrary to the protection of dignity. In view of the connection between protection of dignity and protection of life, from this viewpoint instrumentalisation also applies if the embryo was created for the purpose of giving rise to a pregnancy but is unable to be used for this purpose and is used destructively for other purposes.
- from the viewpoint of those that regard a reduction in the protection of life while preserving protection of the dignity of the human embryo in vitro as possible in principle, legal permission to use such "supernumerary" embryos is regarded as ethically justifiable. This is the case only where it is ensured that protection of the life of the embryo takes precedence over the rights of third parties at whatever level, for as long as the pregnancy for which it was created can still take place, or while other prospects of life may still be offered and if the appropriateness, necessity and proportionality of the research in such embryos has been demonstrated. This pre-supposes high-priority objectives and the link to strict licensing conditions. From the viewpoint of this position, the creation of embryos for the purpose of stem cell derivation cannot, however, be ethically legitimised since it is incompatible with the accepted protection of dignity.
- from the viewpoint of a gradualist position that assumes the start of protection of dignity only in the course of embryonic development and considers that protection of life of the human embryo may be balanced against other considerations, the use of "supernumerary" embryos for high-priority purposes is ethically legitimate. Some representatives even of this position assume that the worthiness of protection to which the embryo in vitro is entitled - in the sense of solidarity of the species or of humanity - excludes the production of embryos for research purposes, unless the appropriateness, necessity and proportionality of this procedure has been demonstrated with regard to the worthiness of protection mentioned.

No consensus exists in our society at present concerning the status of the embryo. The authority to create embryos for purposes other than to bring about a pregnancy and permission to use embryos for purposes other than for their maintenance, even if based on high-ranking medical objectives, could be seen by that part of society which ascribes human dignity and protection of life to the human embryo from the beginning as a threat to the guarantee of human dignity itself.

On the questions of appropriateness, necessity and proportionality, which remain open, on the ethical and constitutional aspects mentioned and the rule that the ethically less controversial means are to be preferred to the more controversial, legal approval of the derivation of stem cell lines from "supernumerary" embryos by modifying the standard of protection of the Embryo Protection Act cannot be recommended.

3.2.2 Regulatory options and recommendations on "therapeutic" cloning

The creation of a totipotent cell by cell nuclear transfer can be regarded as the creation of an embryo, since the cell created in this way has the potential for developing into a human being so that it is regarded as having normative equivalence.

Ethically, for nuclear transfer embryos created for the purposes of stem cell derivation, the protection of dignity and life existing for human embryos in general and discussed here therefore apply in full.

For representatives of the positions that ascribe human dignity to the human embryo from the beginning, the creation of human life for the purpose of benefiting others is an ethically unacceptable offence against human dignity, and the killing of such human life by stem cell harvesting is an unjustifiable interference in the protection of dignity and life, even where high-priority objectives are involved.

For representatives of the positions that assume reduced worthiness of protection, the creation and use of nuclear transfer embryos are ethically justifiable if they comply with the requirements of proportionality, appropriateness and necessity. For many representatives of this position, however, examination of these criteria leads to rejection, particularly with respect to a possible broader application and the associated problems of high egg cell donation requirements.

Moreover, for representatives of the various positions, "therapeutic" cloning represents a first step towards the technology of reproductive cloning and remains open to the danger that the embryo created in this way may be used to give birth to a cloned human being by implantation into the uterus of a woman. Since reproductive cloning represents instrumentalisation not only for the individual human beings concerned but also for the species, contravening fundamental rights arising from human dignity, the danger of misuse - in addition to the other reasons mentioned - must also be regarded as a serious objection to "therapeutic" cloning.

Legally, the creation of a nuclear transfer embryo contravenes the Embryo Protection Act, whether or not this takes place with the intention of stem cell harvesting or reproduction.

In view of the need for certainty, however, legal clarification is necessary for the following reasons:

- nuclear transfer embryos in which foreign egg cells are used are strictly speaking only 99.98% genetically identical and are therefore not clones in the strict scientific sense;
- moreover, cases in which animal enucleated egg cells are used, and cases in which the cell nucleus has been manipulated before introduction into the human egg sac, are not clearly regulated.

Legal clarification should establish that all variants of cloning of human embryos and fetuses, human beings after birth and dead human beings are prohibited by the Embryo Protection Act.

3.2.3 Regulatory options and recommendations on research in imported ES cells

Maintaining the present legal situation in the area of protection of the embryo, the decision must be taken as to whether, while observing the basic right of the freedom of science and research

- separate assessment of the legal and ethical aspects of the derivation and importation of human embryonic stem cells is possible or
- legal and ethical aspects of derivation and importation must be assessed together.

Under criminal law, the importation of pluripotent embryonic stem cells is not limited at present if the intention to import does not lead to criminal involvement in their derivation. This applies both to the use of imported embryonic stem cells for research purposes and also to any possible future therapeutic use. No statement is made, however, concerning the conformity of importation with the spirit of the Embryo Protection Act.

Debatable points, however, are

- whether toleration of regulated importation of existing human embryonic stem cell lines can prevent the killing of further embryos, since research in existing human embryonic stem cell lines is sufficient to obtain new information or
- whether toleration of importation does not also imply toleration of the method of derivation, since research with embryonic stem cells cannot be separated from their derivation and
- whether the production of new stem cell lines and the killing of further embryos is not set in motion if demand increases and if it should emerge that existing stem cell lines are neither quantitatively nor qualitatively adequate[320] and
- whether this research, should therapeutic benefit seem possible, will lead to "therapeutic" cloning.

For the first of these points, a regulatory system of approval is discussed, linking the approval of importation with a mandatory demonstration of appropriateness, necessity and proportionality and preventing extension to new stem cell lines, and requiring the following conditions to be satisfied:

- Restriction to embryonic stem cell lines created prior to a certain deadline (in accordance with the list drawn up by President George W. Bush);

[320] Aspects discussed are the possibly inadequate ability of existing stem cell lines to proliferate, possible contamination by culture media that contain mouse cells, or the need to produce stem cell lines with specific genetic and immunological characteristics.

- Restriction of use to research for priority purposes that cannot be achieved by other research measures. The general priority criteria would have to be established by the legislator, since the concept of protection of life would also be valid here;
- Coupling to demonstration that the stem cells have been derived only from those embryos not created especially for stem cell harvesting but were cryopreserved for the purposes of IVF treatment and were "supernumerary" or permanently orphaned and that the genetic "parents" have given their consent after having received full details of the purpose of the research and other relevant information.
- Linking to quality assurance and monitoring criteria;
- Documentation and publication requirements;
- Prohibition of commercialisation.

Legally, the requirement for approval of this kind would constitute acceptable regulation of the research activity in terms of establishing a safe balance between the freedom of research and the necessary avoidance of jeopardising fundamental values protected by the constitution, such as human dignity and the right to life. Regulation of the conditions under which importation is permitted should not, as for example in the USA, draw a distinction between public and private research. In other words, the conditions under which importation is permitted are to be regulated by law. Only then are they binding for private sector research. A further requirement would be a transparent control authority legitimised by the State.

For advocates of the view that considers it possible in relation to human embryos in vitro to balance the protection of life while respecting human dignity, importation can be approved if the imported stem cell lines are derived from "supernumerary" embryos and if they were derived with the informed consent of the parents. This applies in particular where importation is limited strictly to existing stem cell lines. Such approval, in addition to fulfilment of the criteria mentioned above, does also require demonstration of the high priority of the research objectives and the lack of alternatives to the research methods used to achieve these objectives. The dilemma arising as a result of importation, involving exploitation of the killing of embryos tolerated abroad though prohibited in this country, is acceptable to advocates of this position only if the appropriateness, necessity and proportionality of such importation and research in embryonic stem cell lines can be demonstrated.

If one proceeds from the gradualist position of reduced worthiness of protection for the human embryo, the importation of human ES cell lines is ethically legitimate. Here again, however, a suitable balance must be found between the existing worthiness of protection of the embryo recognised by this view and the high priority of the research objectives; moreover, the appropriateness, necessity and proportionality of importation must be demonstrated.

Ethically, the importation of stem cell lines derived from human embryos cannot be reconciled with the position that from the outset the human embryo is entitled to human dignity and

therefore deserves unlimited protection. The Embryo Protection Act also proceeds from this view. In this context, examination of the conditions for a legally binding import ban should be attempted. It is difficult ethically to draw a distinction between criteria for the protection of embryos outside Germany and those within Germany. Irrespective of the fact that it is legally possible to assess derivation separately from importation, such separate ethical evaluation carries the risk of destabilising the legitimisation of embryo protection.

Some of the members of the Study Commission are of the opinion that both the German Bundestag as the legislator and the Federal government as the executive should use and implement all available opportunities to combat the killing of embryos, including an import ban. These members hold the view that it is impossible to prevent the killing of further embryos by means of import regulation limited to the existing stem cell lines and other restrictive criteria. Such a regulation would in fact not only place Germany among the potential users of existing stem cell lines but would also help to give impetus to the demands already detected in the scientific community for better quality stem cell lines and for the derivation of stem cell lines within Germany itself. Importation would create a demand that would induce and legitimise a corresponding supply, leading to the destruction of further human embryos. However since, in the view of all those advocating the above position, a ban should be retained on the use by third parties of human embryos, to maintain consistency the importation of cell lines arising from behaviour that should be banned should also be prohibited.

Should an import ban based on the protection of dignity and life not prove feasible, other advocates of a ban might find tolerable a closely regulated import arrangement under the strict licensing conditions mentioned above, in the context of an ethical evaluation which sees this as the lesser evil ("minus malum" assessment). An important argument here is the view that the killing of further embryos would be prevented by restriction by law to the existing stem cell lines. This applies in particular where importation is for the purposes of research required only as an interim stage, which makes the future derivation of such cells from human embryos unnecessary and is itself already restricted to existing stem cell lines. The legislator has the opportunity, by clearly restricting legally permitted imports to existing cell lines, to suppress a demand for additional cell lines and remove the inducement to kill further embryos for importation. It would be necessary to ensure that this would not give rise to any change in the Embryo Protection Act with a view to conditional approval of the production of stem cell lines within Germany which would then make use of the import criteria previously introduced.

Regulatory alternatives

The German Bundestag Study Commission on the Law and Ethics of Modern Medicine, in view of the ethical conflicts, continues to regard the derivation of stem cells from embryos involving the destruction of human life as unjustifiable. Members are unanimous that the killing

of embryos for research purposes must be prevented. The Study Commission is in favour of maintaining the high level of protection provided by the Embryo Protection Act.

On the question of the importation of human embryonic stem cells for research purposes, two lines of argument exist within the Study Commission.

Both positions share the view that the necessary regulations must apply equally to the public and to the private sector. They should therefore be placed on a legal footing.

Argument A:

The Study Commission, respecting all arguments, declares itself opposed to the importation of human embryonic stem cells. Its opinion is therefore that the German Bundestag and the Federal government should take all possible measures to prevent the importation of human embryonic stem cells.

The Study Commission regards the use of human embryos for research purposes, even if this takes place abroad, as ethically unjustifiable and scientifically not sufficiently well founded. The necessary basic research can be conducted adequately with stem cells of other origins (embryonic stem cells from primates, cord blood stem cells, adult stem cells, etc.), without opening the door to the misappropriation of human embryos.

Argument B:

Following the deliberations of the Study Commission it seems doubtful whether a complete ban on the importation of human embryonic stem cells derived from embryos abroad can be established on the basis of constitutional and European law. The importation of human embryonic stem cells is therefore to be tolerated under strict conditions. Adherence to these conditions is to be monitored by a State-authorised control authority whose operations are open to scrutiny.

The necessary prerequisite to the permissibility of importation, in the view of the Study Commission, is in particular the following: restriction of imports to the currently existing embryonic stem cell lines derived from cryopreserved “supernumerary” embryos (specific deadline to be defined as in the Bush regulation of 9 August 2001); demonstration of the appropriateness, necessity and proportionality of the research project for which the import application is made; demonstration of qualified informed consent.

Under these strict licensing conditions within an ethical assessment, importation is tolerable, particularly since limiting the permissibility of importation to currently existing stem cell lines will prevent the killing of further embryos for research purposes.

This import regulation is to be linked to the guarantee of continuing protection of the embryo in Germany at its existing high level.

Argument A[321]
Volker Beck
Rainer Beckmann
Priv.-Doz. Dr. Kathrin Braun
Ilse Falk
Hans-Josef Fell
Prof. Dr. Heinrich Fink
Prof. Dr. Linus Geisler
Dr. Sigrid Graumann
Ulrike Höfken
Hubert Hüppe
Dr. Otmar Kloiber
Monika Knoche
Helga Kühn-Mengel
Götz-Peter Lohmann
Prof. Dr. Ernst Luther
Prof. Dr. Therese Neuer-Miebach
Claudia Nolte
Prof. Dr. Johannes Reiter
René Röspel
Dr. Gerhard Scheu
Dr. Ingrid Schneider
Dr. Ilja Seifert
Matthäus Strebl
Dr. Margit Wetzel
Dr. Wolfgang Wodarg
Dr. Michael Wunder

Argument B
Volker Beck
Dr. Sabine Bergmann-Pohl
Hans-Josef Fell
Ulrike Höfken
Prof. Dr. Ludger Honnefelder
Werner Lensing
Dr. Carola Reimann
Margot v. Renesse
Ulrike Riedel
Prof. Dr. Edzard Schmidt-Jortzig
Prof. Dr. Erika Schuchardt
Prof. Dr. Klaus Tanner

[321] Cf. Members of the Study Commission on the Law and Ethics of Modern Medicine.

4 Embryonic germ cells (EG cells)

The preparation of EG cells from aborted embryos of fetuses is permissible in Germany as long as the cell lines produced are not found to be totipotent, i.e. capable of forming a complete human individual.[322] Embryos or fetuses which have already died and are used for EG cell derivation are not subject to the requirement of protection of life under basic law.[323] However, the "Guidelines for the use of Fetal Cells and Fetal Tissues" issued by the German Medical Association (Bundesärztekammer) in 1991 do apply.[324]

The removal of other embryonic or fetal tissues from aborted embryos or fetuses for stem cell derivation is not analysed further in this connection. However, it is subject to the same ethical and legal problems in relation to the harvesting of cells.

The special attention being paid to embryonic germ cells is based on the observation of their pluripotency and therefore their particular suitability for stem cell production. The Commission did not discuss the specific use of embryonic germ cells for the culture of gonad or germ cell replacement or for the creation of embryos. This would require separate ethical and legal consideration.

4.1 Ethical and legal problems

4.1.1 Connection with termination of pregnancy

The connection between the derivation of germ cells from embryonic of fetal tissue and the performance of termination of pregnancy was regarded as a fundamental problem in dealing with EG cells.

It is essential that measures which could lead to an increase in the number of terminations of pregnancy should be avoided. There are fears, however, that the possibility of tissue donation could be seen as an additional justification for terminations of pregnancy. Women who are still

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[322] Only in this case would they fall, according to § 8 (1) ESchG, under the area of protection of this Act. Otherwise the Embryo Protection Act does not apply since it covers only the period up to nidation of the embryo or totipotent cell in the uterus.

[323] The term "aborted fetuses", used below means aborted dead fetuses.

[324] Bundesärztekammer 1991.
By contrast, the comments of the Central Ethics Committee at the German Medical Association on the transfer of nerve cells into the brains of humans (Bundesärztekammer 1998b) deal only with the transplantation of fetal nerve cells into the brains of humans. However, this does not relate to research with EG cells. The comments recommend that, in view of the ethical problems involved in harvesting fetal tissues and in the light of promising alternative methods of treatment under development, treatment trials and clinical studies relating to the transfer of fetal nerve cells into the brain of human beings should be suspended for the time being.

undecided whether or not to terminate a pregnancy might be more likely to decide on termination if they felt that the tissue donation could help in the development of treatments for previously incurable diseases. The derivation of EG cells would then be indirectly responsible for increasing numbers of terminations of pregnancy (legitimisation argument).

The connection between EG cell derivation and termination of pregnancy is difficult to resolve in practice because the derivation of cells depends on a morally dubious course of action which requires justification. Scientists could become "accomplices" in moral dubious behaviour by producing EG cells and using them for research (complicity argument).

Termination of pregnancy and subsequent use of the embryonic or fetal tissue for research or therapeutic purposes can also be regarded as unacceptable instrumentalisation of human life (instrumentalisation argument). A requirement for this argument, however, is that the termination of pregnancy was for the purpose of providing embryonic or fetal tissue. A similar direction is followed by fears that society's attitude to human life could change if aborted embryos or fetuses were used for the derivation of EG cells.

These arguments, taken from the discussion on the use of fetal tissues for transplantation purposes[325], can also be applied to the use of aborted embryos or fetuses for stem cell harvesting. The arguments are based on the assumption that there is a link between the decision to terminate a pregnancy and the decision to donate tissue. A decisive factor in assessing the production of EG cells from embryonic or fetal germ cells is therefore the question of whether separation of the two decisions, and therefore separation of the ethical assessment of terminations of pregnancy and the EG cells obtained in this way, is possible.

The separation of decisions on termination of pregnancy and on EG cell harvesting is therefore essential in order to prevent a possible influence on the time or method of termination to create particularly favourable conditions for the derivation of embryonic or fetal germ cells. These concerns have been expressed in particular on the use of fetal tissue in transplantation medicine, since in this case seven to eight terminations of pregnancy must take place as nearly as possible at the same time, in order to obtain sufficient tissue for a transplantation and this tissue must also be damaged as little as possible during the termination.[326] A different situation exists, however, with respect to the derivation of germ cells for the production of EG cells. No co-ordination in time of a number of terminations is necessary and for research purposes a few embryos or fetuses from terminations of pregnancy should be adequate. However, modified methods of termination, associated with higher health risks for the woman, are required for the derivation of EG cells and the termination must take place in the 5th to 11th week of pregnancy.

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[325] Cf. e.g. Ach et al. 2000, P. 140 ff.
[326] Schneider 1995, P. 212 f.

4.1.2 Informed consent

The question of who should approve the use of embryonic or fetal tissue following terminations of pregnancy has already been discussed in detail in connection with the subject of transplantation medicine. Some authors assume that, by her decision to terminate, the woman has lost her right to decide on the further use of the aborted embryo or fetus.[327] Regulations on embryonic or fetal tissue transplantation in other countries have overwhelmingly adopted the view that only the woman can decide on possible further use after the termination of pregnancy.

The role of the father in informed consent is largely unregulated. While regulations exist, for example, in the USA which give the father the opportunity to veto the agreement of the woman, the 1991 German Medical Association guidelines assume the right of disposal for the parents in the preamble, though in the text of the guidelines only the informed consent of the pregnant woman is covered by the regulations.[328]

A clear separation of the decision to terminate pregnancy and the decision to donate the embryonic or fetal tissue is possible only if the decision on tissue donation is taken independently of termination of pregnancy.[329]

The prerequisite for separating the decision on termination of pregnancy from that on tissue donation is that the possibility of donating embryonic or fetal tissue is raised only after the decision to terminate the pregnancy has finally been taken. If the material is to be of any biological use, however, the decision to donate must be taken before the termination. Benefits that could affect the decision must not be offered. An attempt should be made to separate the two issues, in terms of both personnel and administrative arrangements. The extent to which such regulations on the procedure in practice can be met, however, is doubtful, particularly since staggering of the procedure would be associated with an additional burden for the patient.[330]

The guidelines on the use of fetal cells and fetal tissue provide for the possibility of linking a statement of purpose to informed consent to tissue donation after a termination of pregnancy. The pregnant woman can give instructions regarding the extent of cell and tissue removal and also the general nature of their use.

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[327] Cf. Burtchaell 1988.
[328] Cf. Bundesärztekammer 1991, Section. 4.5. According to Laufs 1999, § 130, note 43, the use or destruction of embryonic or fetal organs or tissues for research purposes requires the written consent of the genetic parent.
[329] Cf. the situation relation to transplantation: Ach et al. 2000, P. 155 f.
[330] Ach et al. 2000, P. 156.

4.1.3 Effects on the social situation of women

Effects on the social position of women are to be taken into account with regard to the use of embryonic or fetal tissue for the production of EG cells and also in connection with the transplantation of such tissue.

It is feared that women could increasingly be regarded as "suppliers of raw materials" who make tissues available for purposes of research or transplantation. The hopes being awakened regarding therapeutic prospects for EG cells could also lead to women feeling obliged to give their consent to the use of embryonic or fetal tissue. In connection with transplant medicine it was pointed out that, particularly with an increasing demand for embryonic or fetal tissue, subtle pressures to donate tissue following termination of pregnancy could be imagined which could even lead to direct or indirect commercialisation and "a depersonalisation of women as exploitable cultivation units".[331]

Consideration must also be given to the psychological stress on women who give up dead fetuses for EG cell derivation after termination of pregnancy and on those women who make "supernumerary" embryos available from in-vitro fertilisation for the production of ES cells. Some foresee greater problems for the woman in the donation of embryonic or fetal tissue, since having experienced the pregnancy a biographic relationship already exists between the woman and the fetus. Others hold the view that release of an already dead fetus is less stressful for the woman than a decision on the life of an embryo.

4.2 Regulatory options and recommendations

With regard to the derivation and use of fetal cells and fetal tissue from aborted fetuses, the 1991 guidelines of the German Medical Association[332] and a 1998 decision by the Central Ethics Committee at the German Medical Association on the transfer of nerve cells into the human brain[333] apply.

In the decision of the Central Ethics Committee of the German Medical Association, a critical view is taken of the removal and use of fetal nerve cells from aborted fetuses. It called in practice for a moratorium on the use of fetal cells from aborted fetuses in general.[334] The main points highlighted by the Central Ethics Committee were:

- the difficulties with the practical arrangements for harvesting fetal cells or tissues, which cannot yet rule out the possibility that the decision to use these tissues may affect the decision to terminate pregnancy, and

[331] Schneider 1995, P. 229.
[332] Bundesärztekammer 1991.
[333] Bundesärztekammer 1998b.
[334] Cf. Footnote 324

- the lack of clarity in the legal situation.[335]

Ethically, the use of aborted embryos or fetuses for the harvesting of stem cells can be approved, if at all, only provided that the following principles, set up in the 1991 guidelines of the German Medical Association on the use of fetal cells and fetal tissues, are applied to this area:

- The embryo or the fetus must be dead; accordingly, derivation criteria must be taken into account.
- Guarantee of the independence of the decision to abort and consent to use;
- Separation of personnel and administration of the releasing and using institution;
- Linking to the informed consent of the woman;
- Determination of the informed consent criteria, in particular exclusion of a restrictive designation of recipients;
- Exclusion of commercial interests and practices;
- Documentation and
- Approval by a public regulated Ethics Committee.[336]

Both the request by the German Bundestag on 25 June 1997 to the Federal Government, "to submit a Bill as soon as possible regulating the transplantation of fetal tissue"[337], and also the decision by the Central Ethics Committee of the German Medical Association in 1998 have made it clear that there is a need for legislative regulation.

The removal and use of cells and tissues from embryos or fetuses should be regulated in this law including the harvesting of stem cells.

In view of the increase in possible uses for embryonic or fetal tissue, particularly in the area of EG cells, revision of the legal regulations after a few years appears to be necessary. This applies in particular with regard to the social situation of women. The framework for these revisions may be specified by the legislator and should aim to make the developments as transparent as possible. The work of revision may be entrusted to authorities or Committees, the membership of which should be specified by the legislator.

[335] For example, §168 StGB regulates the theft of a dead fetus, but not its use with consent; the Transplantation Act applies explicitly only to fetal tissue and organs.
[336] Bundesärztekammer 1991.
[337] Final decision and report of the Health Committee (14th Committee): Draft of a law relating to the donation, removal and transfer of organs (Transplantation Act - TPG), BT Printed paper 13/8017.

5 Neonatal stem cells from cord blood

5.1 Ethical and legal problems

5.1.1 Right of ownership/right of disposal

After birth, the placental tissue including the residual placental blood ("cord blood") is normally discarded although, in view of its medical use, it has now become a "raw material". The question of the right to disposal of the cord blood is still a matter of controversy with respect both to the right of ownership and to personal rights. It has also been pointed out that parents could claim ownership if they were to accept the costs of harvesting or storing the stem cells. Similar arguments could also be advanced by the operators of private cord blood banks or by the public health authority, if the derivation or storage of stem cells were publicly funded.[338]

Aside from the legal questions, however, parents in practice do decide on the disposal of the cord blood. They may decide on specific (named recipient) or non-specific (unspecified recipient – allogeneic) donation of the cord blood, its storage or disposal.

5.1.2 Informed consent

The joint "Guidelines for the Transplantation of Stem Cells from Cord Blood (CB = Cord Blood)"[339] of the German Medical Association and the Paul Ehrlich Institute provide for parental approval following the provision of information, ideally during the pregnancy. In any case, however, the declaration of consent in writing, at least of the mother, must be obtained for a donation of cord blood before it is forwarded to the processing centre.

In current practice, the mother is asked before delivery whether she agrees to storage in a cord blood bank of the stem cells from the cord blood of her newborn infant for possible later use. The procedure for harvesting the cord blood and the tests to be carried out on the blood are explained to her.

These are generally specific or non-specific donations, given for altruistic reasons. Private companies offer storage facilities for the commercial storage of cord blood supposedly for the purpose of an autologous transfusion, for the individual's own benefit.

The tests performed on the blood relate mainly to characteristics necessary for safe transplantation, such as determination of the cell composition, blood group and tissue typing

[338] Gordijn / Olthuis 2000.
[339] Bundesärztekammer & Paul Ehrlich Institut 1999.

and the presence of infection parameters. An attempt is made by taking a careful case history to determine the existence of hereditary diseases. In theory, genetic tests could also be performed on the cells, e.g. in order to rule out the transfer of genetically transmitted diseases in transplantation. It remains to be seen whether separate permission for further genetic analysis will need to be obtained from the biological parents.[340]

The question of handling information obtained in this way relating to the state of health of the child and its biological parents are largely the same, with regard to data protection, right to know/right not to know, as those associated with genetic testing in general. Anonymisation of the blood preparations has been discussed in connection with the use of cord blood. This would not only solve the question of consent for specific genetic tests and the associated decision concerning utilisation or non-utilisation of the information from the test, but would also avoid the question of the obligation to divulge known genetic diagnoses to third parties (insurance companies, employers). Assuming that the storage periods for cord blood could be 20 to 30 years, donations already frozen will be affected by these developments.

5.1.3 Reprogramming to totipotency

Both the use of stem cells from cord blood for bone marrow transplantation and also the possibility of using stem cells from cord blood to create other tissue by transdifferentiation or reprogramming can be compared with the use of adult tissue-specific stem cells. Because of their immaturity, stem cells from cord blood may prove more suitable for reprogramming than adult stem cells. A manipulation of stem cells leading to totipotent cells will be regarded as prohibited by the Embryo Protection Act. If neonatal cells are transformed by reprogramming to the totipotent stage, the stem cells from cord blood are subject to all the concerns mentioned with regard to ES cells.

5.1.4 Economic aspects

At present, cord blood banks may be financed by private payments from parents, private or state donations and payments by individual private health insurance schemes.

A distinction must be drawn basically between the storage of cord blood for autologous use at a later point in the life of the child and use for third parties (allogeneic transplantation). At the international level, not all privately financed cord blood banks are restricted to autologous use. Nor are all publicly financed institutes restricted to allogeneic transplantation.[341] In Germany, the privately financed cord blood banks currently provide storage capacity for stem cells for autologous transplantation only.

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[340] Gordijn / Olthuis 2000.

[341] In allogeneic transplantation, the cord blood is transferred to a recipient with the closest possible match of tissue characteristics.

If cord blood banks and the storage of stem cells is supported by public funds or health insurance schemes, the aim must be a just distribution of the donated stem cells amongst all patients who can profit from treatment with the cells. In order to ensure adequate access, attempts to obtain stem cells from cord blood would need to be intensified considerably. It should be born in mind here that voluntary donation of cord blood is risk-free for the donor, ethically uncontroversial and inexpensive for society.

It is becoming possible to an increasing extent to derive or produce a number of different stem cells from cord blood. These can probably be used for a variety of treatments as well as for bone marrow transplantation. There therefore appears to be a need to extend the harvesting, collection and storage of donated cord blood and to standardise the costs of storage, if clinical use should be confirmed on completion of the experimental phase.

The commercial offer to build up stocks of cord blood on an individual basis could give rise to unfounded expectations in the parents of newborn infants. Commercial models have been developed in recent years based on the hopes of parents that their child might in later life be cured, in the event of a serious illness, by means of the preserved neonatal stem cells. Parents could be made to feel that they were placed under moral pressure, particularly by promotional brochures, to do something apparently essential for their child that they could hardly refuse.[342] The "Guidelines for the transplantation of stem cells from cord blood (CB)" of the German Medical Association and the Paul Ehrlich Institute make the following comment:

> There is at present no known medical indication for the storage of autologous CB preparations and it is therefore unnecessary at the present time.[343]

5.2 Regulatory options and recommendations

The use of neonatal stem cells as allogeneic or autologous transplant material appears ethically less controversial. Collection of and research with neonatal stem cells should therefore be promoted in a deliberate and appropriate manner. Information obtained in this way should help to evaluate further the "neonatal stem cells" resource, to estimate the financial funding necessary for their collection and use, to discover the scope of their possible applications and to determine the possible implications for their equitable distribution. Apart from these aspects, however, the need remains for legal clarification with regard to the rights of disposal of cord blood, data protection issues and principles for the financing of cord blood banks.

Clarification is necessary of the extent to which the current power of disposal of mothers/parents over cord blood, particularly with respect to its use for the benefit of third parties, can be regarded as adequate or whether, for example, the child must reach the age of consent before the cord blood is released for allogeneic purposes. In practice, however, these

[342] Gordijn / Olthuis 2000.
[343] Bundesärztekammer and Paul Ehrlich Institute 1999.

concerns become relevant only if scientific evidence were to suggest that the autologous use of neonatal stem cells is superior to allogeneic use.

Consent to the collection of cord blood for stem cell derivation should also include the decision as to whether this is a specified or unspecified donation. Information from the genetic data gathered can then be used in full or with a reduced timescale or parameters. Parents could also be given the right not to receive this information. This should be regulated in law.

Cord blood banks can be financed either publicly or privately. It is possible, as at present, to retain both forms in parallel. When deciding on the financing of cord blood storage, the prospects of success of treatments made possible by storing cord blood will play a central role. Public financing of cord blood banks is particularly desirable and appropriate for reasons of social solidarity, if stem cells from cord blood can be used for allogeneic transplantation.

Adequate information, taking account of the current state of knowledge, on the potential of stem cells from cord blood should be provided at national level, e.g. by the central federal authority for health education.

6 Adult stem cells (AS cells)

6.1 Ethical and legal problems

6.1.1 Informed consent in the use of AS cells

The decisive advantage in using AS cells for transplantation purposes is the possibility of using the patient's own cells, so avoiding immunological rejection reactions. Until the method is standardised, the legislation must assume treatment trials or experimental studies that require particular care in the obtaining of informed consent in view of the risk involved. However, if the transdifferentiation or reprogramming of autologous AS cells is not a possibility, allogeneic (heterologous) AS cells may also be used for the benefit of third parties. The procedure is similar in some respects to that of blood donation. If potentially risky invasive techniques are involved, however, the procedure is more closely comparable with the live donation of organs or tissues such as bone marrow.

6.1.2 AS cells as post-mortem tissue donation

If the initial indications that AS cells can also be harvested after death are confirmed, this procedure would have to be treated in the same way as organ donation, with the consequence that a specific consent procedure is necessary.[344]

6.1.3 Reprogramming to totipotency

Should tissue specific AS cells be available for widespread medical use, methods of reprogramming (mutation back to a pluripotent stage) and transdifferentiation (development to a cell type not part of the original development spectrum of the cell) must be prohibited. The possibility of obtaining totipotent cells from adult stem cells by means of complete reprogramming is not yet documented in medical science. Should this be possible, however, or even unavoidable in certain reprogramming techniques, this would come into the sphere of regulation of the Embryo Protection Act. In this case all ethical and legal considerations discussed in relation to embryonic stem cells would apply.

[344] Particular features may result in the case of brain stem cells.

6.2 Regulatory options and recommendations

The derivation and use of adult stem cells, insofar as these occur in the autologous context and without reprogramming to totipotency, do not present legal or ethical problems and are adequately regulated by existing laws and guidelines.

Derivation and use in the allogeneic (heterologous) context requires legal clarification of the rules of consent for the donor and recipient and also regulation of allocation and exclusion of commercial interests, in parallel with the Transplantation Act.

In relation to the use of cadaveric tissue, experience of the Transplantation Act reveals a tendency towards presumed consent so that personal consent is moving increasingly into the background while agreement by third parties is increasing. To counter this tendency, the willingness to donate organs – including the potential possibilities of treatment with stem cells – should be promoted more strongly in future by means of education and public discussion. The collection of allogeneic (heterologous) cells for the benefit of third parties from the bodies of minors should be ruled out, in order to avoid from the outset any tendency that a child might be created with a view to the derivation of AS cells for a relative.

Insofar as reprogramming of AS cells to totipotency is to take place, the terms of the Embryo Protection Act should be clarified.

From the ethical viewpoint, the promotion of research in adult stem cells, particularly their proliferation, reprogramming and transdifferentiation, should continue to be given priority in Germany.

7 Appendix I: Possible therapeutic uses of stem cells

Target organ, tissue	Disease	Cell type needed; expandable in differentiated form?	Differentiation and expansion of human adult precursor cells / AS cells	Differentiation from murine ES / EG cells	Differentiation from human ES / EG cells	Experimental transplantation in small or large animal models	Clinical studies
Bone marrow, peripheral blood	Auto-immune disease, leukaemias	Haematopoietic precursor cells expandable within limits	$CD34^+$ haematopoietic progenitor cells from bone marrow or from cord blood	**+** (1)	***?** (2)		Clinically tried for years (3, 4)
Vessels, vascularised tissue, heart valves, venous valves	Vascular occlusion caused by arteriosclerosis, valve defects,	Endothelial cells expandable	$CD34^+$ haematopoietic progenitor cells from bone marrow or from cord blood	**+** (5)	***?** (2)	(6-8)	**-**
		Fibroblasts	MSCs (9)	+	***?**(10)		
		smooth muscle cells	MSCs **?**	**+** (11)	**?**		
Brain, spinal cord	Parkinson's disease, Alzheimer's disease, multiple sclerosis, spinal injuries, paraplegia	Neurones, glial cells, terminally differentiated cells not expandable	Stem cells from subventricular zone and hippocampus (12, 13)	* (14, 15)	***?** (2, 10, 16-18)	(19-21)	Transplantation of embryonic or fetal neuronal cells (22, 23)
Retina	Blindness	Neurones, glial cells not expandable	Only demonstrated to date in mice and rats (24-26)	**?**	**?**	**-**	**-**
Skeletal muscle	Injuries, various myopathies	Skeletal muscle cells Differentiated muscle fibres not expandable	Skeletal myoblasts (satellite cells) MSCs **?**	**+** (27)	***?** (2, 10, 16-18)	(28, 29)	**-**
Cardiac muscle	Myocardial infarction, AV block, congenital malformations	Myocardial cells adult myocardial cells not expandable	MSCs **?** (30-32)	**+** (33-36)	***?** (2, 16-18)	(37)	**-**
Bone	Fractures, degenerative bone disease	Osteocytes calcified osteocytes not expandable	Periosteal cells (38-40) MSCs (41-43)	**+** (44, 45)	***?**(10)	(46, 47)	

Target organ, tissue	Disease	Cell type needed; expandable in differentiated form?	Differentiation and expansion of human adult precursor cells / AS cells	Differentiation from murine ES / EG cells	Differentiation from human ES / EG cells	Experimental transplantation in small or large animal models	Clinical studies
Cartilage (joints, trachea, ear)	Cartilage defects, injuries	Chondrocytes (expandable)	Periosteal cells (38, 40), MSCs (41-43)	* ? (48)	*?(10)		In clinical use for approx. 10 years (49, 50)
Skin	Burns	Differentiated cells not expandable, though skin contains epithelial stem cells	Epithelial stem cells from skin (51, 52)	* ? (53, 54)	?		In clinical use for many years (55, 56)
Liver	Cirrhosis, etc.	Hepatocytes not capable of proliferation, in spite of high in-vivo regeneration potential (oval cells) no appreciable expansion achieved yet *in vitro*	Oval cells (57, 58), $CD34^+$? (59) In-vitro expansion to appreciable extent not yet possible	?	*?(18)	(60)	-
Pancreas	Diabetes	ß-cells not expandable	Possibly existence in rat and mouse (61, 62)	* (63), (64) (Rhesus monkey)	?	(62)	
Gut, stomach	Crohn's disease, malignant diseases	Intestinal epithelium differentiated cells not expandable, though gut contains epithelial stem cells	Epithelial stem cells from intestine; isolation only successful in mouse to date (65)	*?(64, 66)	*?(10)	-	-
Kidney	Renal failure	Mesangial cells expandable	?	?	*?(10)	-	-
Ureter / bladder	Congenital malformations, malignant disease	Urothelium expansion possible	?	?	?	(67, 68)	-

Overview of cell types that can be differentiated from stem cells, the diseases that can be treated with these and the tissues / organs that may be capable of generation. Numbers in brackets indicate the relevant literature.
(Prepared by Dr. Ulrich Martin for the Konrad-Adenauer Foundation, Status 02/2001)

*	= Data not yet confirmed; in spite of investigations, doubt persists regarding creation of functional cell types
*?	= Data not yet confirmed; very little experimental information available
CD34	= specific surface molecule
ES/EG	= Embryonic stem cells/primordial germ cells
MSC	= Bone marrow cell (Marrow Stromal Cell)
murine	= originating from the mouse
Progenitor cell	= precursor cell

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8 Appendix II: Overview of legal regulations in selected countries

8.1 Australia

8.1.1 Relevant sources of law

- Ethical Guidelines on Assisted Reproductive Technology (1996)
- Code of Practice for Units Using Assisted Reproductive Technology (1996) (published by the RTAC, Reproductive Technology Accreditation Committee)
- National Statement on Ethical Conduct in Research Involving Humans (1999)

8.1.2 Overview

Embryo research (general)	**Research in human embryonic stem cells (ES cells)**	**"Therapeutic" cloning**	**Derivation of cell material from fetuses (EG cells)**
• Embryonic research for the benefit of others is possible if ➢ the germ cell donors have agreed ➢ it promises major scientific benefit ➢ the number of embryos to be used is determined in advance	• Derivation of human ES cells and research in these is permitted	• permitted	• permitted

8.1.3 Comments

The table shows the regulations (acts, statements, guidelines, codes) at federal level only. Responsibility for regulation, however, lies primarily with the individual federal states, of which South Australia, Victoria and Western Australia have so far approved their own regulations.

8.2 Israel

8.2.1 Relevant sources of law

- Law prohibiting genetic intervention (Cloning of humans and genetic modification of reproductive cells), 1999

8.2.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	"Therapeutic" cloning	Derivation of cell material from fetuses (EG cells)
• the following are prohibited by law: 1. reproductive cloning of a human being 2. genetic modification by the use of germ line cells (Germ Line Gene Therapy)	• Derivation of human ES cells and research in these is permitted	• permitted	• no prohibition ➢ permitted

8.2.3 Comments

Apart from the prohibitions shown above, these areas of research are subject to no restrictions.

8.3 Japan

8.3.1 Relevant sources of law

- Anti-cloning Law, June 2001

8.3.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	"Therapeutic" cloning	Derivation of cell material from fetuses (EG cells)
• the bioethics committee of the Commission for Science and Research is opposed to the production of embryos for research purposes - only "supernumerary" embryos are to be used • the Life Ethics Committee of the Japanese government sees the need for development of embryo and stem cell research but at the same time finds that only precise legal regulation will allow sensible and justifiable use of these areas of research	• not legally regulated	• not legally regulated	• no prohibition

8.3.3 Comments

Apart from the new Anti-cloning Law, which prohibits reproductive cloning, there are no legal regulations in Japan in the area of embryo and stem cell research. Regulation and control of research is the responsibility of individual ministries, that is, the executive. The permissibility of research is basically linked by these to various conditions, such as the high priority of the purpose and lack of alternative.

Guidelines on the treatment of embryos should be issued after the Anti-cloning Law by November 2001.

8.4 Canada

8.4.1 Relevant sources of law

- Memorandum from the Canadian Government, 1995
- Human Reproductive and Genetic Technology Act, 1996

8.4.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• de facto, research in embryos is essentially permitted up to day 14 of development. • de facto, the use of gametes or embryos is possible only with the approval of the donor • de facto, the creation of embryos for pure research purposes is prohibited	• permitted • Derivation of human ES cells from "super-numerary" embryos is permissible	• permitted, but no official procedure known	• permitted

8.4.3 Comments

There are no legal regulations on embryo and stem cell research, but only general ethical guidelines which leave a great deal of room for manoeuvre and impose only inadequate sanctions in the event of contravention. At the initiative of the Canadian Institute of Health Research (CIHR), guidelines on stem cell research are to come into force shortly. In addition, an anti-cloning law is currently planned that will expressly prohibit reproductive cloning of human beings. Furthermore, a national ethical monitoring committee is to be set up in order to monitor research developments for their ethical justifiability.

8.5 United States of America (USA)

8.5.1 Relevant sources of law

- Public Health Act, 1996
- Guidelines for Research Using Human Pluripotent Stem Cells (Guidelines for research in human embryonic stem cells), 2000

8.5.2 Overview

Embryo research (general)	**Research in human embryonic stem cells (ES cells)**	**"Therapeutic" cloning**	**Derivation of cell material from fetuses (EG cells)**
• Prohibition of state funding ➢ for research in embryos produced for this purpose, destroyed or exposed to more than necessary risks ➢ research in embryos produced by therapeutic cloning ➢ Purchase and sale of dead embryos or fetuses	• Research in ES cells permissible • Actual human research projects are assessed individually (see below) • the guideline for state-funded research specifies that ES cells may only be used if ➢ they were derived from "supernumerary" embryos voluntarily donated for this purpose ➢ informed consent was obtained from the donor with clear mention of the intended use ➢ IVF and ES cell research are not to be carried out by the same person • state funding for research with ES cells possible because these are not embryos in the sense of the legal definition but pluripotent cells[345] • no state funding for the production of ES cells[346] • Privately funded ES cell research or production is regulated in 10 federal states and sometimes very strictly[347]	• no state funding • Bill prohibiting human cloning passed by House of Represen-tatives	• state funding of research with tissue from dead fetuses, observing suitable safety arrange-ments

[345] Rabb 2001.
[346] NIH 2000c.
[347] Europäisches Parlament 2000, p.47-50.

8.5.3 Comments

In the USA, the regulatory approach in the area of embryo research is different because of the fundamental difference as compared with the German legal system. There are considerably fewer legally binding regulations at federal level, influence being exerted to a greater extent through budgetary decisions[348].

State regulation in the area of embryo research at federal level therefore falls into two areas: that of research based on complete and even partial state funding, which is comprehensively regulated and controlled and that which is exclusively privately funded. Ethical standards of protection are expressed primarily in funding guidelines and are specifically incorporated in the above guidelines of the National Institute of Health (NIH). ES cells are legally classified here under xenotransplantation.[349] The Human Pluripotent Stem Cell Review Group, a committee made up in accordance with legislative requirements of experts and lay individuals, takes decisions on specific sponsorship applications. On 9 August 2001 the American President permitted the state funding of research with those embryonic stem cell lines whose derivation had already begun before this time.[350]

In the private sector, however, the state exerts no influence, provided that no offence is committed against laws of higher precedent or general legislation, such as the Constitution or Federal law. On 31. 7. 2001 the House of Representatives passed a federal law making cloning of embryos, fetuses and human beings for whatever purpose a criminal offence[351]. The law only requires ratification by the Senate. Effective regulations for wholly privately funded research also exist at individual State level - at the beginning of 2001 this was the case in 10 States and in others laws were in preparation. Florida State regulations, for example, prohibit some procedures including the culture of embryonic cell lines and basic research in ES cells. It is notable that, on explosive issues such as the production of ES cells, private research companies regard themselves as being under a certain amount of public pressure. For that reason, apart from one published exception[352] they have therefore so far probably observed the legalities for the production of ES cells laid down in the State sponsorship regulations.

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[348] The proportion of state funding of medical research projects is considerably greater in the USA than in Germany. More effective influence is therefore possible in the USA by this means.

[349] "Transplanting into human stem cell preparations derived from founder cells that have been in direct, intimate contact with nonhuman animal cells constitutes xenotransplantation - the use of organs, tissues and cells derived from animals to treat human disease." (National Institutes of Health 2001, p. 204).

[350] Bush 2001.

[351] Richwine 2001.

[352] The deliberate creation of an embryo for the purpose of harvesting a stem cell line was reported for the first time in July 2001 (Lanzendorf 2001).

8.6 France

8.6.1 Relevant sources of law

- Law No.94-654, 29.6.1994 ("les lois bioéthiques")
- supplemented by Decree No.97-613, 27.5.1997

8.6.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• Research in embryos for the benefit of others is prohibited in principle • it is permitted in exceptional cases after authorisation and with the prior written consent of the genetic parents only, 1. if it takes place within the first seven days of development AND 2. if it is for the direct benefit of the embryo OR 3. if it leads to an improvement in methods of medically assisted reproduction, by expanding knowledge of the physiology and pathology of human reproduction • Creation of research embryos and research in them is prohibited	• Research with ES cells already isolated is not regulated by law ➢ no ban, so permitted • Derivation of ES cells prohibited	• prohibited	• permitted

8.6.3 Comments

Revision of these legal regulations is currently being discussed in France, following a proposal by the Comité Consultatif national d'Ethique set up in 1983 by the French President that research in aborted fetuses, in embryos in vitro and therapeutic cloning should be permitted under certain strict conditions[353].

8.7 Great Britain

8.7.1 Relevant sources of law

- Human Fertilisation and Embryology Act, 1990

[353] Comité Consultatif national d'Ethique 2001.

- Code of Practice of the Human Fertilisation and Embryology Authority, 1990
- Human Fertilisation and Embryology (Research Purposes), 2001

8.7.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• Research in human embryos is permissible up to day 14 after fertilisation for certain purposes if: ➢ written consent has been obtained from both genetic parents ➢ production of and research with embryos has been licensed • Research objectives for which licences may be obtained are: ➢ improvement of infertility treatment ➢ obtaining of information concerning the causes of miscarriage ➢ obtaining of information on hereditary diseases ➢ development of more effective contraceptive methods ➢ development of methods for the detection of gene and chromosome anomalies prior to implantation • Since 31.1.2001 also: ➢ obtaining of information on the development of embryos ➢ obtaining of information on serious diseases ➢ transfer of that knowledge into the development of treatment for serious illnesses • The agreement of the HFEA (approval authority) and the cell donor must be obtained • No other equally suitable research possibilities must exist	• Production of and research in ES cells is permitted	• permitted	• permitted

8.7.3 Comments

In Great Britain, the technology of reproductive medicine began with the birth of the first test tube baby in 1978. The 1990 Human Fertilisation and Embryology Act and the supplement on

therapeutic cloning issued in 2001 set up a comprehensive system of legal regulation based largely on the safeguards of statute law supervised by an authority (Human Fertilisation and Embryology Authority, HFEA), whose approval procedure takes decisions on each individual research project and monitors these. This regulates both the public and the private sector.

There is also a body known as the Human Genetics Commission (HGC) which advises the Government on questions of gene technology. This monitors the scientific and legal framework. The effective interaction of these two areas is monitored and guaranteed in this way[354]. There are also further bodies who are responsible for issuing information and regulations in the sphere of genetic engineering.

8.8 Norway

8.8.1 Relevant sources of law

- Norway: Act relating to the application of biotechnology in medicine (No. 56 August 5th 1994)

8.8.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• prohibited	• permitted	• prohibited	

8.8.3 Comments

The law provides for regular evaluation at intervals of five years. The Government has prepared a Bill for introduction.

8.9 Austria

8.9.1 Relevant sources of law

- Austria: Fortpflanzungsmedizingesetz (Law relating to "medically assisted reproduction") dated 1992

[354] for further information see www.hgc.gov.uk.

8.9.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• prohibited	• permitted	• prohibited	

8.9.3 Comments

There is no explicit regulation of cloning techniques in the law governing reproductive medicine in Austria. However, on the basis of the regulations of §§ 1, 3 and 9 of the law, it can be seen that all types of cloning are regarded as prohibited in Austria. Only the number of egg cells necessary for likely and acceptable medically assisted reproduction may be fertilised.

8.10 Russian Federation

8.10.1 Relevant sources of law

- Law on the state regulation of the use of gene technologies (1996)
- Supplement to the law regulating gene therapy dated 1996 (2000)
- Government Order on the registration of all technically modified organisms (2001)
- Law relating to the transplantation of organs

8.10.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• Not regulated by law • Sale and purchase of embryos and fetuses prohibited by interpretation of the law on transplantation	• permitted	• not regulated	• not regulated

8.10.3 Comments

Russian research is very active in this sphere of modern medicine. Research in this area is practically all state-sponsored. There are various laws for the regulation of this research and these allow great latitude. Areas subject to no regulation are largely exhausted scientifically[355]. The Committee for the protection of health and sport in the Russian parliament prepared a draft law for consultation which was introduced by the Government which proposes a one to five-year ban on human cloning and on the import and export of cloned human embryos.[356]

8.11 Switzerland

8.11.1 Relevant sources of law

- Switzerland: 1999 Federal Constitution
- Switzerland: Federal Act on medically assisted reproduction (Reproductive Medicine Act, FmedG), which came into force on 01.01.2001

8.11.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• prohibited	• permitted	• prohibited	

[355] PID, for example, is not subject to legal regulation but is performed in 14 hospitals including two hospitals for sex determination or for the detection of any genetic disease.
[356] Foreign Ministry of the Russian Federation 2001;
The section on the Russian Federation is based on information from Prof. Dr. habil. Alexander Butrimenko, Department of Science and Technology at the Embassy of the Russian Federation in Germany.

8.11.3 Comments

Whether the importation of ES cells into Switzerland is legally permitted is a matter of hot debate. The Swiss National fund for the Promotion of Scientific Research wishes to support research with human embryonic stem cells in future and has taken the decision to promote importation against the decision of the National Ethics Council.

Apart from straightforward legal regulation by the Reproductive Medicine Act, comprehensive safeguards exist in the Constitution (cf. Art. 119 II a: All types of cloning and interference with the genetic make-up of human germ cells and embryos are prohibited.).

8.12 Spain

8.12.1 Relevant legal sources

- Law on the techniques of assisted reproduction, 1988

8.12.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• Research in embryos is permissible within the first 14 days after fertilisation, if ➢ the genetic parents have given their consent in writing ➢ it is applied research (diagnostic, therapeutic purposes) or basic research ➢ it is not carried out in viable pre-embryos ➢ no other equally suitable means (animal studies) can be used	• Research with existing ES cells permissible, these must have been created under the conditions shown (left hand column) and be used for the purposes mentioned (left hand column)	• prohibited	• permitted

8.12.3 Comments

The 1988 legal regulation was the subject of an – unsuccessful – investigation by the Constitutional Court for contravention of the constitutional protection of human life.

8.13 Germany

8.13.1 Relevant sources of law

- Embryo Protection Act (ESchG), 1991

8.13.2 Overview

Embryo research (general)	Research in human embryonic stem cells (ES cells)	Therapeutic cloning	Derivation of cell material from fetuses (EG cells)
• prohibited • embryo and totipotent cell equivalent under law	• research permissible • derivation of stem cells prohibited	• prohibited[357]	• permitted

8.13.3 Comments

The Embryo Protection Act (ESchG) of 13 December 1990, which came into force on 1. 1. 1991, is an Act prohibiting the misuse of assisted reproduction and of the human embryo in vitro (§§ 1 to 4) and prohibiting certain procedures (§§ 5 to 7) such as germ line modification, cloning, formation of chimeras and hybrids. This has the nature purely of criminal law and therefore provides only partial regulation of the medical application of the technology.

The Embryo Protection Act prohibits the use of an embryo for a purpose other than its maintenance. Research in embryos is therefore prohibited. Totipotent cells are equivalent to an embryo under the terms of the Act. Embryonic stem cells, however, which are no longer totipotent, are not covered by the Embryo Protection Act. Use of and research with these is therefore not prohibited.

[357] However, reference is made to loopholes in the regulations: Bülow 2000, P.47; Onducu 2001.

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10 Glossary

Allele

The various expressions of a gene are described as alleles. For each gene, two alleles are present in the ? *cell nucleus* (one on the set of chromosomes inherited from the mother and one on that inherited from the father), which may be either identical (? *homozygous*) or different (? *heterozygous*)

Allogeneic transplantation

Transfer of cells, tissues and organs between genetically non-identical members of the same species (? *autologous transplantation*)

Autologous transplantation

Transfer of the body's own cells or tissues (or transfer of cells, tissues and organs between genetically identical patients) (? *allogeneic transplantation*)

Blastocyst

Early stage of embryonic development, in humans at about day 4 to 6 after fertilisation, consisting of approx. 100 to 200 cells. The outer cell layer (? *trophoblast*) is later involved in the formation of the *placenta*, the inner cell mass (? *embryoblast*) consists of ? *precursor cells* for the subsequent ? *embryo*

Blastomere

Cells arising from cleavage of the ? *zygote*

Cell nuclear transfer

? *Nuclear transfer*

Cell nucleus

Constituent of the cell containing the ? *chromosomes*

Chimera

Use of this term is not standardised. Life form or tissues from cells of different ? *genotypes* (? *hybrid*)

Chimeric

Cells and groups of cells arising from the transfer of cell nuclei of human origin into egg cells of animal origin are described as chimeric with respect to their genetic material because in addition to human nuclear DNA they also contain ? *mitochondrial* ? *DNA* of animal origin

Chromosomes

Components made up of ? *DNA* and ? *proteins* found within a cell nucleus, containing the genetic information; their aggregation is visible with a microscope during the processes of cell division. The number and configuration of chromosomes is species-specific. In humans, each somatic cell contains 23 pairs of chromosomes: 22 pairs of autosomes, one pair of sex chromosomes (? *diploid* set of chromosomes); each ? *nuclear cell* contains only one set of chromosomes (? *haploid* set of chromosomes)

Cryopreservation

Deep-freezing at -196°C of organic tissues, sperm and egg cells capable of regeneration

Differentiation

Development of a cell into a specific cell type. The differentiation of ? *stem cells* can be initiated by the addition or removal of certain growth and differentiation factors (? *transdifferentiation*)

Diploid

Adjective defining a set of chromosomes in which two sets of each chromosome are present. ? *Somatic* cells, unlike nuclear cells in humans, contain a diploid set of chromosomes (? *haploid*)

DNA (deoxyribonucleic acid)

Molecule consisting of ? *nucleotides* in the form of spiral chains (double helix) wound around its own axis, carrying the genetic information of an organism

Dopamine

Substance acting as a messenger between ? *neurones*; present in abnormally low concentrations in individuals with Parkinson's disease

Dopaminergic

Responding to ? *dopamine*

Embryo

In medical terms, the embryo is the fertilised egg during the period of organ development in the womb, i.e. approximately from the point of ? *nidation* into the mucous membrane of the uterus up to the end of the third month of pregnancy. After organ development up to the end of pregnancy, the term ? *fetus* is used (? *zygote*)

In the report, the embryonic stages ? *zygote*, ? *morula* and *blastocyst* are also referred to as the embryo.

According to § 8 of the Embryo Protection Act (ESchG), the embryo is defined as the fertilised viable egg cell from the time of fusion of the nuclei

Embryo adoption

Transfer of an ? *embryo* to a woman who is not the genetic mother, in the context of an adoption-like procedure

Embryo splitting

Process of artificial formation of a multiple pregnancy, in which the embryo at the two-cell to ? *blastocyst* stage is divided by mechanical separation of the group of cells into two or at most four parts.

Embryoblast

Inner cell mass of the ? *blastocyst*, from which the embryo develops.

Embryoid body

Cell colonies made up of cells which are not finally differentiated, which can be formed in culture from ? *stem cells* and contain cells of all three ? *germ layers*

Enucleation	Removal of the ? *nuclear genome*, for example from an egg cell, in preparation for acceptance of a donor cell or a donor cell nucleus.
Epigenetic	Collective adjective describing those influences on the development of an organism that are not directly coded in the genetic information and may result from interactions between genetic factors or between genetic factors and environmental factors
Epithelial cells	Cells that cover external or internal surfaces of the body and develop from the outer of the three ? *germ layers*; for example, skin cells
Extracorporeal	Occurring or taking place outside the body
Fertilisation	Making fertile (? *in-vitro fertilisation*)
Fetus	In medical terminology, the unborn offspring after completion of organ development (? *embryo*)
Gamete transfer	Transfer of germ cells (? *gametes*)
Gametes	Male or female sex cells (? *germ cells*)
Gene expression	Conversion of genetic information to a gene product, usually a protein
Genome	Totality of all genetic information in a cell
Genome analysis	Investigations at various levels (? *phenotype* analysis, chemical analysis of proteins, cytogenetic analysis, ? *DNA* analysis), the direct purpose of which is to obtain conclusive information on the genetic make-up of a living organism
Genotype	Collective term for all genetic information determined in the genes of an organism, that can be manifest in the ? *phenotype*
Germ cell	Sex cell of an organism, e.g. egg cell, sperm cell (? *gametes*)
Germ layers	General name for the cell layers arising in early embryonic development, known as the ectoderm, endoderm and mesoderm from which all structures arising in the further development of the ? *embryo* develop

Germ line	All cells in a cell line from the fertilised egg cell down to the egg and sperm cells of the offspring produced from it; also the egg cell from the insertion or penetration of the sperm cell to the point of fertilisation completed with fusion of the nuclei
Gonads	Sex organs (ovaries and testes) and the cells of the sex glands prior to sexual differentiation
Gradualism, gradualist argument	Moral philosophic argument claiming a correlation between embryonic or fetal development and moral rights to protection and therefore allowing differentiation with regard to the moral status of embryos and fetuses
Haematopoietic	Relating to the formation of blood cells
Haploid	Designation for a set of ? *chromosomes* in which each chromosome is present only once. The ? *germ cells* of a human being, unlike the somatic cells, exhibit a haploid set of chromosomes (? *diploid*)
Heterozygous	Having mixed hereditary information for a particular gene, i.e. the two ? *alleles* of the gene are not identical
Histocompatibility	Tissue compatibility (? *tissue typing*)
Homozygous	Having pure hereditary information for a particular gene, i.e. the two ? *alleles* of the gene are identical
Huntington's chorea	Incurable, hereditary neurological disease of late onset, usually appearing between the ages of 30 and 45 and leading to involuntary abnormal movements and mental deterioration.
Hybrid	Use of this term is not standardised. Living organism arising from a cross between parents of different species. In hybrids, all ? *somatic* cells are genetically identical (? *chimera*)
Immune reaction, immunological reaction	Reaction of an organism by means of the body's defence system (immune system) after contact with substances that are recognised as foreign
Immunosuppression	Artificially induced suppression or weakening of the ? *immune reactions* of an organism, for example to prevent the rejection of tissues or organs in transplant surgery

Imprinting	Different expression of a gene (? *gene expression*) or of a region of a gene due to the parental origin of an ? *allele*
In vitro	Outside the living organism or outside the body, in the laboratory (? *in vivo*)
In vivo	In the living organism, within the body (? *in vitro*)
Informed consent	Voluntary authorisation of a treatment or participation in a research project by individual patients or subjects
Intrauterine	Located or occurring within the womb
In-vitro fertilisation (IVF)	The joining of egg and sperm cell outside the body (? *in vitro*); in-vitro fertilisation is one of the established procedures in reproductive medicine
Juvenile diabetes	Genetically conditioned form of diabetes mellitus occurring in childhood, due to progressive destruction of the insulin-producing cells of the pancreas (type I diabetes)
Markers	Specific characteristics of cells
Mesenchyma	Cell tissue (embryonic connective tissue) arising from the middle of the three ? *germ layers* and from which the structural and connective tissues, muscle cells, vascular endothelia etc. develop
Mesenchymal	Belonging to the ? *mesenchyma* or relating to this
Mitochondria	Cell organelles found in the cytoplasm of a cell and having their own small ? *genome* (in humans, 37 genes). Mitochondria are basically responsible for the energy supply to a cell ("power stations" of the cell)
Mitochondrial DNA	Ring-shaped independent ? *DNA* found within the ? *mitochondria*, inherited exclusively from the mother
Morula	Embryonic development stage in which the individual ? *blastomeres* are no longer recognisable but appear as a solid mass of cells

Myelin	Insulating sheath covering certain nerve fibres in a spiral formation. It is responsible for safeguarding conduction of electrical pulses in the nerve. If the myelin sheath is destroyed, conductivity is lost.
Myeloablative	Removing functional bone marrow
Myelosuppressive	Inhibiting bone marrow activity
Neonatal	Relating to the new-born infant
Neurones	Nerve cells
Nidation	Implantation of the fertilised egg cell into the mucous membrane lining the womb, in humans approx. on day 12 after conception
Nuclear genome	The ? *DNA* of the ? *cell nucleus* is known as the nuclear genome
Nuclear transfer	Transfer of a ? *diploid* ? *cell nucleus* into the cytoplasm of an ? *enucleated* egg cell
Nucleotide	Individual ? *DNA* building block, consisting of one of the four bases (adenine, cytosine, guanine, thymine), a phosphoric acid residue and a sugar molecule
Phenotype	External expression of a characteristic arising from interaction between the genetic information (? *genotype*) and environmental influences
Placenta	The structure within the uterus consisting mainly of fetal and to a lesser extent of maternal cells, responsible for the nutrition of the fetus (exchange of metabolic products and gases) and the production of various hormones; is expelled after delivery (afterbirth)
Pluripotency	The capacity of cells or tissues to differentiate under suitable conditions into more than one type of cell or tissue (? *totipotency*)
Post mortem	Occurring after death
Precursor cell	Cell from which a particular cell type develops by means of a series of development stages

Prenatal	Occurring before birth
Prevalence	The number of cases of a disease that are present in a population at one point in time or during one defined period
Primitive streak	The axis of symmetry of the ? *embryo*; prerequisite for the formation of the nervous system
Primordial germ cells	Cells giving rise to the germ cells via a series of development stages. Primordial germ cells, unlike mature germ cells, have a ? *diploid* set of chromosomes. From these, embryonic germ cells (EG cells) may be obtained during the late embryonic or early fetal stage
Proliferation	Multiplication
Pronuclear stage	Condition of egg cells in which, after penetration of the sperm, fertilisation has begun but in which fusion of the nuclei of the egg and sperm cells have not yet taken place
Pseudonymisation	The process by which the data directly identifying a person is changed according to an allocation specification produced for the individual project, so that the pseudonym produced in this way can be reallocated to an actual person only with knowledge of this allocation specification
Reproductive cloning	Procedure for the artificial creation of a multiple pregnancy in which - unlike ? *therapeutic cloning* ? the intention is to give birth to a genetically identical individual
Reprogramming	The returning of a cell to an earlier stage of development (e.g. of a ? *somatic* cell) to a ? *pluripotent* or ? *totipotent* stage, by reversing the functional differentiation processes through which the cell passes in the course of its development and during which the various genes are activated or inactivated
Somatic	Relating to the body
Stem cell line	Stem cells that can be cultivated over long periods in specific culture media and are distinguished by particular characteristics and cell functions
Stem cells	Cells that renew themselves by cell division and are capable of maturing into individual or various cell types (? *differentiation*)

Therapeutic cloning	Process of artificial creation of a multiple pregnancy that remains restricted to the ? *in-vitro* phase and may be used in particular for the derivation of genetically identical sets of cells or tissues
Tissue typing	During tissue typing, various characteristics are determined that together allow an estimation of the compatibility of the donor cells with possible recipients. The HLA characteristics are of particular importance here (? *histocompatibility*)
Totipotency	The terms totipotency and ? *pluripotency* are used in the scientific literature in a non-standardised way: in classical embryology, the totipotency of a cell is understood to mean the ability to develop into a complete individual. Pluripotent cells, however, in the context of classical embryology are capable of developing into various cells, tissues or organs but not into a complete individual. In research into embryonic mouse ? *stem cells*, totipotency is taken to mean the capability of taking part, after injection into foreign ? *blastocysts*, in the creation of all tissues including the germ line. Other definitions of totipotency include the capability of a cell to differentiate into all three embryonic ? *germ layers* or into all cell types of an organism. In the Embryo Protection Act (§8 ESchG) totipotency is defined as the ability to develop into a complete individual.
Toxicity testing	Investigation of a substance with regard to its harmful effects, for example in an animal experiment, a human study or in cell cultures
Transdifferentiation	Development of a cell into a cell type that has not previously formed part of the development spectrum of this cell, without going through the early stages of development by means of ? *reprogramming*
Transfusion	The transfer of blood or blood products from a donor to another individual
Trophoblast	Outer cell layer of the ? *blastocyst*, from which, in the course of development, the embryonic parts of the ? *placenta* arise

Umbilical cord blood, cord blood	Residual blood remaining in the umbilical cord after cutting; contains ? *neonatal* stem cells
Zygote	Fertilised egg cell as the product of fusion of the nuclei of the egg and sperm cells; cell from which embryonic development originates (? *embryo*)

Figure 1

Methods of embryonic stem cell derivation

Development of a human egg cell

Fertilisation of the egg cell **Start of cell division** **Day 2** **Day 3** **Day 4** **Week 6**

Up to the 4-cell stage, the cells are not yet differentiated (totipotent cells)

Specialisation of cells e.g. into precursor cells of organs (pluripotent cells)

Stem cells are **capable of dividing** but are **not differentiated cells.**

1. Derivation of stem cells from artificially fertilised egg cells
2. Derivation of stem cells from the germ cells of **aborted** fetuses (wk. 5-11 of pregnancy)
3. **Cell transfer:** An egg cell from which the nucleus has been removed is fused with a **somatic cell**. Stem cells derived from inner cell mass of blastocyst

Egg cell

The **aim** of derivation of stem cells is to allow the **artificial cultivation of cells** from which cell tissue, e.g. nerve cells, can be developed

Pluripotent cells from the inner cell mass of the blastocyst are taken and cultured in petri dishes

Somatic cell

Figure 2

Cloning

The original

(1) A **somatic cell** is taken from a human being

Egg donor

(2) ***unfertilised egg cell***

(3) The **DNA** is removed From the egg cell

(4) **Cell nucleus** and **egg cell fused** in the laboratory

Variant A: Reproductive cloning

The developing **embryo** is implanted in the womb of a surrogate mother and carried to term

Variant B: "Therapeutic" cloning

Embryonic stem cells are taken from the blastocyst after approx. 4 days and cells or tissues developed from these

Figure 3

Research in embryonic stem cells

1

Stem cell derivation

"Therapeutic" cloning:
An egg cell from which the nucleus has been removed is fused with a somatic cell

or

Harvesting of stem cells from "**supernumerary**" embryos after IVF

or

Harvesting of embryonic stem cells from **aborted fetuses**

2

Blastocyst derivation

Early embryonic stage (approx. 4 days)

Embryoblast

Trophoblast

3 Cell cultures

Pluripotent stem cells
Types of cells and tissues can develop from these

4

Possible applications

Tissue cultures, cell therapy

Parkinson's disease
Nerve cells

Testing of medicines

Heart disease
Heart muscle cells

Diabetes
Pancreatic cells

Leukaemia, Cancer
Bone marrow

Gene therapy research

Source: NIH/MRC