NEK CNE
Nationale Ethikkommission im Bereich Humanmedizin
Commission nationale d'éthique pour la médecine humaine
Commissione nazionale d'etica per la medicina
Swiss National Advisory Commission on Biomedical Ethics

Research involving human embryos and fetuses

Opinion no. 11/2006

Bern, January 2006

Opinion no. 11/2006 was adopted by the Commission on 22 September 2005.

Publication details

Published by: Swiss National Advisory Commission on Biomedical Ethics (NEK-CNE)

Production management: Lic. phil. I Georg Amstutz, NEK-CNE Executive Secretary

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Design and layout: Sandra Bongard, Nidau

Illustration: Edith Christen, Malatelier Hans & Edith Christen, Biel

Copy editing: Georg Amstutz, Csongor Kozma and Markus Christen

Printing: Witschi & Co. Nidau

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The full report is available in German and French. Abridged versions have been published in English and Italian.

Special thanks are due to the NEK-CNE «Embryo Research» Working Group for its editorial work. The Working Group consisted of the following members of the Commission: Dr Margrit Leuthold, Dr Jean Martin, Dr Carola Meier-Seethaler, Professor Alexandre Mauron, Prof Christoph Rehmann-Sutter and Dr Brigitte Weisshaupt.

The Swiss National Advisory Commission on Biomedical Ethics is also grateful to the numerous individuals and institutions that were directly or indirectly involved in the preparation of this publication, including in particular:
Minou Friele, MA (Düsseldorf), who drafted the sections on the current state of the ethical debate; Boris Bögli (Biel), who helped to prepare the scientific sections; Dr Laurence Vindevoghel (Zurich) and dipl. biol. Raschid Setoud (Bern) who worked as scientific consultants and Professors Alois Gratwohl (Basel), Wolfgang Holzgreve (Basel), Bruno Imthurn (Zurich), Hansjakob Müller (Basel) and Roland Zimmermann (Zurich), who reviewed the scientific sections.

Contents

Introduction

Subject of the report

These recommendations were prepared in response to a request made by the Federal Department of Home Affairs on 20 October 2003 for comments on a series of specific questions relating to embryo research that arose in the context of the drafting of the Human Research Act. In addition to fundamental issues, the set of questions concerned research involving germ cells and their precursors, inseminated oocytes, in vitro embryos, in vivo embryos/fetuses, embryos/fetuses that are to be aborted, embryonic/fetal tissue deriving from abortions or miscarriages and, finally, «embryo-like» organisms.

Owing to the exceedingly complex nature of the topic, the preparation of responses within the Commission proved to be a lengthy process. In the course of the winter and spring of 2004/2005, draft opinions were submitted to the Swiss Federal Office of Public Health (SFOPH) for consideration in three parts. For the present report, intended for the general public, the Commission's conclusions were reorganized and supplemented by sections outlining the scientific/medical background and the current state of the ethical debate. The sections explaining the reasons for the positions adopted were substantially expanded, and the recommendations were reviewed and revised in plenary sessions.

The arguments and controversies that shaped the Commission's deliberations are summarized as considerations. The recommendations take the form of approved texts; in cases where the text was not endorsed by all the members of the Commission, this is duly indicated. The sections dealing with the current state of research/practice and the ethical debate were prepared by external experts, and reviewed and expanded by members of the Commission.

Chapter I: Fundamental reflections

1.2 Principles underlying the Commission's evaluation

Two of the most widely discussed and most controversial questions in ethical and biopolitical debates of recent years are (a) whether any research on human embryos and fetuses is permissible and (b) if so, what types of research. In this area, attitudes within society vary widely. Some people are fundamentally opposed to research involving nascent human life on moral or religious grounds. Others take the view that research on human embryos offers legitimate opportunities to obtain new scientific and medical knowledge, but call for a transparent and fair system of controls. The analyses and recommendations of the NEK-CNE are based on the following fundamental considerations:

1. The **potential** of germ cells and their precursors, of embryos, and of individual cells from embryos or fetuses is taken to be their inherent capacity to develop, under appropriate conditions, into a human being. Here, the term «human being» denotes on the one hand the «biological being» (a «something») and on the other the «personal being» (a «somebody»), and the term «potential» refers to the capacity for development of such cells or organisms in both respects. These entities' need for and claim to protection, or their moral status, is partly (but not exclusively) dependent on this capacity. An embryo does not lose its claim to protection merely because its capacity for development is restricted.
2. If one considers capacity for development (i.e. potential) to be a central factor in the recognition of the embryo's moral status and dignity, one need not invoke the metaphysical thesis that an embryo which can become a person must therefore already be treated as a person. This thesis (known in the debate as the «potentiality argument») played no part in the Commission's deliberations. Also disregarded was the thesis that the embryo's moral status is grounded in the genome (the individual's genetic information). A large proportion of the Commission inclines to the view that development is a gradual process, in the course of which **the ethical claim to protection** grows in line with the increasing complexity of the organism. A majority of the Commission assumes that the embryo's dignity and claim to protection exist from the outset, i.e. from the moment of fertilization, and subsequently increase. Recognizing the embryo's «dignity» means protecting the embryo for its own sake. Its claim to protection is intrinsic. A minority considers the early embryonic stages – like germ cells – to be, in the legal sense, an «object». However, this minority nonetheless defends the embryo's claim to protection in view of the human being that arises from the embryo and in view of the parents whose bodies are the source of the germ cells and who hope to have a child.
3. Within the Commission (as in society), there is a **plurality** of approaches – reflecting different world views – to the ethical issue of the moral status of the embryo and the fetus; however, this need not always result in disagreement at the level of practical recommendations. Certain recommendations may be supported by a variety of justificatory approaches.
4. With regard to the embryo's **entitlement to protection**, two lines of argument can be identified which differ in their emphasis but also overlap. Both of these approaches are represented in debates within the Commission.
    a. The deontological approach takes the embryo's entitlement to protection to be intrinsic. It therefore makes no distinctions as to how the embryo was created or what it may become. It tends, for example, to support a ban on therapeutic cloning.

b. The consequentialist approach is more open to differentiation, since the broader context is taken into account (e.g. circumstances, intentions, awareness of consequences, etc.). However, this approach does not necessarily argue for the rejection of legal restrictions. It is also possible to make a consequentialist case against therapeutic cloning.

5. For the Commission, the embryo's **claim to protection** does not rest on a single principle. In particular, the obligation to protect the embryo does not derive solely from its potential for development. Additional, contextual factors include the possibility of being transferred to the womb to establish a pregnancy, the intention underlying the embryo's creation, the absence of risks of malformation (e.g. following diagnostic testing for chromosome anomalies), or the application of the cell nuclear replacement method to create an embryo.
6. In certain areas, the **complex and dynamic nature of the ethical questions** addressed in this Opinion makes it difficult to arrive at a wholly rational and consistent position, accommodating all the relevant viewpoints. Those aspects that are clear to the Commission provide the basis for its recommendations. In cases where ethical questions have yet to be adequately clarified, the Commission adopts a cautious stance.
7. The term **embryo** (from the Greek embruon, derived from the verb bruein «to swell») refers to the early developmental stage of an organism. Usually, a human embryo is created by the fusion of an egg and a sperm cell. The oocyte has a tendency to divide. However, if it is not fertilized, the results of a parthenogenetic development of this kind have a disorganized form. More than half of all embryos of apparently normal appearance (arising from fertilization) have no chance of developing to term. They are lost spontaneously as a result of failure of implantation or chromosomal disorders. Development can also be artificially induced by means of cell nuclear replacement. If these methods are also taken into account, the concept of an embryo comprises the following three elements: the embryo arises (1) from an oocyte or from a somatic cell returned to a totipotent state (at present, the latter remains a theoretical notion). This development requires (2) either fusion of the oocyte with a spermatozoon or an alternative form of stimulation, as represented by parthenogenesis or cell nuclear replacement. The embryo develops (3) in accordance with the human blueprint. A capacity for development is considered to be part of the definition of the term «embryo». However, a product of fertilization (or a product of cell nuclear replacement and similar artificial procedures) is also regarded as an embryo even though it lacks the capacity to develop beyond a given embryonic stage. Nonetheless, the actions that are to be permitted or not permitted in the case of an embryo of this kind may differ from those involving embryos that are capable of development.
8. A majority of the Commission assumes that we owe **ethical respect and consideration** to ex vivo embryos. Society has an obligation to protect them from interventions that are not in the interests of their successful further existence. The interests of research, as such, lie in generating reliable knowledge and not, in principle, in promoting the welfare and survival of an individual embryo. Ethical respect and consideration for in vitro embryos and their claim to protection are based on the fact that they are wholly dependent on protection, and that they are entities which can develop into human beings if they are transferred to a woman's womb.
9. The term **moral status** is generally used to refer to the intrinsic dignity and integrity of the embryo. However, the embryo is also entitled to protection on ethical grounds since it bears a relation to the child resulting from subsequent growth. These relationships (like the potential for use or abuse that may exist) are «extrinsic» and are taken seriously by the Commission. They are just as relevant to the recognition of the embryo's moral claim to protection as the embryo's intrinsic value or dignity.

10. In the course of embryonic development and pregnancy, various more or less distinct stages can be identified: fertilization, fusion of the pronuclei, the morula (ball of cells), the blastocyst, implantation, the beginning of differentiation of subsequent fetal tissue after the blastocyst stage, the appearance of the primitive streak, various stages of brain development, the completion of organogenesis, the beginning of extrauterine viability, birth, and further intermediate stages. These thresholds may provide a basis for the application of certain legal norms. For such norms to be applicable, the law must tie the existence of different rights and obligations to characteristics that are objectively identifiable. However, the Commission would emphasize that these points are **artificially defined** within a gradual process of development. If they are based on observable phenomena, they may still have a certain plausibility.
11. The law must specify the point at which the developing human being becomes a **legal subject**: from what point is the fetus a subject of fundamental constitutional rights? According to legal doctrine, full legal subjecthood essentially begins at birth. From the time of birth onwards, a concrete relationship exists between mother and child. The child becomes a person in its own right, to be treated legally as a specific individual. It is thus admitted as a member of society. The Commission can see no reason to depart from this position. It does not consider legal subjecthood to begin at the moment of fertilization, even if (a majority of) the Commission assumes that even the earliest embryonic stages have a claim to protection, which continues to grow until legal personality is acquired at birth. The legal position does not, however, require any discontinuity in moral status. From an ethical perspective, in the Commission's view, the transition is fluid. Birth does not mark the beginning of the ethical claim to protection. Gradual growth in the ethical claim to protection is compatible with the acquisition of an independent legal status at birth.
12. The fact that a process may also occur **naturally**, i.e. without human intervention, does not entail the ethical legitimacy of an artificially induced process of the same kind. For example, while two embryos in utero may spontaneously form a chimera, this does not automatically make experimentally induced chimerism an ethically acceptable research method.
13. The use of cells or tissues from a human body for research purposes may only be permitted on the condition that **informed consent** has been granted. Justification needs to be provided not for the donors' right to be fully informed or for their right of veto, but for any exceptions to this rule. This requirement is applicable to all research projects in which human cells or tissue are used, and in particular for experiments involving germ cells.
14. Another general requirement for research involving human cells and tissues is that it should not be possible for the research objective to be achieved **by any other, less ethically problematic means.**
15. The primary goal of research is to acquire new knowledge. Researchers, legitimately, claim a right to **freedom of research** with regard to subject matter and methods. Research should therefore only be restricted by society for good reasons. Society may also benefit from this freedom, since it can never be known in advance what findings of basic research may yield beneficial applications. At the same time, it should be borne in mind that research, and basic research in particular, receives significant financial support from the state. The authorities, for their part, are accountable for the way in which they allocate the funds at their disposal. To this extent, scientists cannot claim immunity from society's vigilant (and critical) scrutiny.
16. Fundamentally, the state has a right and a duty to consider the social relevance and utility of research. Reflections of this kind are especially important in cases where research raises sensitive ethical issues or explores areas at the boundaries of what is considered

acceptable by society. Research involving human embryos lies in this boundary zone, primarily on account of the object of study (rather than its subject matter or goals). It is a **responsibility of the law** to define the limits of the availability of human life for research. However, the definition of research objectives and methods is not a matter for the law, but is to be left to the freedom of research. This means that, within its specific responsibilities, research is required – on the basis of its expertise – to draw attention to possible limits of its activities. It also has an ethical responsibility for its own objectives and methods.

Chapter II: Germ cells

2.3 Considerations and recommendations of the NEK-CNE

With the exception of synthetic germ cells, which according to recent findings can be derived from stem cell cultures, germ cells have been the subject of research for many years. Such research has focused especially on chromosome aberrations and in recent years also on polar body diagnosis. In the view of the NEK-CNE, particular consideration should be given to the following points in the ethical assessment of germ cell research:

1. Gametes, whether natural or produced in vitro, and primordial germ cells are cells that have the ability to pass on their genetic material to subsequent generations. This property of carrying genetic information and their capacity to fuse, thereby producing new human life, sets them apart from other living human cells. Their moral significance is based on the fact that they are indispensable to the development of future generations. Future generations could be affected by the risks arising from germ cell manipulation.
2. From a purely technical viewpoint, a woman's egg cells only become available in special circumstances: following surgical removal of the ovaries, when oocytes are extracted for research purposes by follicular aspiration after hormonal stimulation, or when they are left over after an in vitro fertilization procedure. Undertaking follicular aspiration when a different procedure has to be carried out in the abdominal cavity is prohibited without the consent of the woman concerned. (With the patient's consent, this scenario would be theoretically possible; however, as it would involve a combination of two quite different surgical objectives, complicating the decision-making process both for the main procedure and for oocyte donation, it should be rejected.) Oocytes are highly complex cells with substantial biological potential. In addition, they are scarce, as supplies are not replenished during a woman's lifetime. In contrast, sperm cells have a simpler structure and are available in large quantities. However, like the removal of egg cells from a woman, the retrieval of sperm from a man is a sensitive matter, intruding on a sphere of privacy. All the various situations in which germ cells are to be recovered call for particular respect for the women and men concerned. The use of germ cells for research purposes requires regulation in various respects. Although male and female germ cells differ in terms of their biological endowment and relative accessibility and scarcity, they are equally deserving of protection with regard to use for research purposes.
3. Germ cells are more deserving of protection – i.e. entitled to be handled with care – than other cells. This is due to their special biological potential: they are a prerequisite for the development of new life. However, the Commission does not consider germ cells to have intrinsic dignity or a right to life.
4. In 2003, stem cell researchers managed for the first time to identify embryonic germ cells, i.e. the precursors of egg and sperm cells, in a human embryonic stem cell culture. It may be assumed that, at some point in the future, it will become possible with appropriate stimulation for stem cells produced in vitro to differentiate into egg and sperm cells with the capacity for maturation and fertilization. As a result, gametes and – if these were successfully fused – also embryos would become available to researchers in large (theoretically unlimited) quantities without any further need for recourse to donors. The question thus arises of how such gametes produced in vitro, and embryos created from these cells, are to be regarded from an ethical viewpoint. Any difference between the ethical status of gametes produced in vitro and that of natural gametes could only be based on differences in the likelihood of their giving rise to a new generation of human life or in their capacity to do so.

This capacity remains to be elucidated. As long as it is unclear, there is no convincing basis for distinguishing these cells from natural gametes. Accordingly, the principle of equal treatment is to be applied. The woman (or the couple) that donated the embryo used to obtain a stem cell culture would logically have to be treated in the same way as an oocyte or sperm donor. She/they would have a right to be informed and her/their consent would have to be sought.

On the basis of these considerations, the NEK-CNE takes the view that research involving egg or sperm cells must essentially be subject to the following rules:

a) The research objective cannot be achieved using any other type of cell.
b) The woman/man gives informed consent to the use of her/his gametes.
c) Hormonal ovarian stimulation with a view to oocyte donation solely for research purposes is not permissible.

In addition, for gametes produced in vitro the following rules are to be complied with:

a) The fertilization of gametes produced in vitro for research purposes is equivalent to the fertilization of natural gametes for research purposes. It remains – rightly, according to the majority of the NEK-CNE – prohibited. However, if it were to be demonstrated that embryos from artificial gametes lack the capacity for development, the question would have to be reconsidered. In this case, a minority of the NEK-CNE would approve of the creation of embryos for research purposes using gametes produced in vitro. For the proponents of this view, the claim to protection or a prohibition is based not on the embryonic stage in itself, but on the capacity for further development.
b) The woman (or the couple) that donated the embryo used to obtain a stem cell culture from which egg or sperm cells are grown in vitro should be treated in the same way as an oocyte or sperm donor. She has (or they have) a right to be informed and her/their consent to this use must be sought.
c) A special situation arises if the stem cells were anonymized. This would mean that the gametes produced in vitro are also anonymous and informed consent cannot be obtained from anyone. In this case, the NEK-CNE can see no fundamental objections to the gametes being used for research purposes (but not for the creation of embryos). The requirement for informed consent lapses automatically if there is no longer anyone whose genetic data should be protected.
d) On the question of whether it should be permissible for anonymized gametes produced in vitro to be used for fertilization, the majority of the Commission expresses its opposition. Respect is owed to the embryo in its own right, not because it is derived from persons who are themselves to be respected. Only the minority that considers the embryo to be an «object» can also accept the possibility of embryos being created for research purposes in these circumstances.

Chapter III: In vitro embryos and embryo-like entities

3.3 Considerations and recommendations of the NEK-CNE

Preliminary note: The central ethical questions discussed in this section concern inseminated oocytes and embryos produced by artificial means. Issues relating to «surplus embryos» and stem cell research are discussed in the next chapter.

3.3.1 Inseminated oocytes

Essentially, all of the considerations presented for oocytes in the previous chapter also apply to **inseminated oocytes** (pronuclear stage). In addition, the following question is to be discussed: the fact that the fertilization process does not consist of a single event (fusion of nuclei) gives rise to the issue of the special legal status of inseminated oocytes as compared with fertilized embryos. There is an ethical and legal tendency to classify entitlement to protection into clearly differentiable stages. Within the complex fertilization process, there is therefore a need to define criteria upon which such a classification can be based. The criterion specified under existing law is the fusion of the nuclei of the two gametes (karyogamy). However, the question arises whether this criterion is ethically convincing. Compared with gametes, inseminated oocytes have an increased potentiality, since the penetration (or introduction) of the spermatozoon ushers in the development of a new human life, with the completion of the fertilization process. The process is irreversible and is merely delayed as long as the inseminated oocyte remains cryopreserved. Accordingly, its extrinsic value (with regard to the creation of a human being) is greater than that of egg and sperm cells. As fusion of the male and female pronuclei occurs within a few hours after the thawing of frozen inseminated oocytes, a fundamental distinction between their moral/legal status and that of embryos is ethically unconvincing. Biologically, a greater difference exists between egg and sperm cells on the one hand and inseminated oocytes on the other than between the latter and embryos following the initiation or completion of karyogamy.

«Embryo-like» organisms include the products of therapeutic or non-reproductive cloning, created by transferring a cell nucleus into an enucleated oocyte («cloned embryos»); the products of parthenogenetic cell division («parthenogenetic embryos», also known as «parthenotes») or of androgenesis; and finally the products of combinations of embryonic cells from different individuals («chimeras») and hybrids. Additional scenarios involving embryo-like entities created in the laboratory cannot be ruled out. As the ethical issues raised by these various scenarios may differ markedly, the NEK-CNE recommends that a nuanced approach should also be adopted by the law.

The development of an embryo proceeds in a series of steps. Fundamentally, therefore, the NEK-CNE is inclined to accommodate a gradualist perspective in the ethical assessment. The following conclusions should be noted:

a) The NEK-CNE calls into question the absolute validity of the karyogamy criterion for drawing distinctions as to the moral entitlement to protection. It seems difficult to justify the view that the cell nucleus (or DNA) is of exclusive significance in defining individuality.
b) Consequently, the NEK-CNE recommends that in regulations less of a distinction should be made between the stage immediately preceding karyogamy and the stage following its completion, and that the handling of pronuclear stages in research should also be carefully regulated.

c) At the same time, a majority of the NEK-CNE does not consider karyogamy to be an event marking the beginning of personhood. It prefers other models for describing the emergence of an ethical claim to protection – models assuming that the dignity of the embryo develops gradually and that personhood arises at a later stage. Although the view that pronuclear stages are more comparable to fertilized embryos does not give rise to any absolute prohibitions on research, it does entail a requirement that they should be handled with care. The pronuclear stages are nothing more – but also nothing less – than embryonic/cellular structures that are in the process of forming and have the potential to form an embryo.

3.3.2 Therapeutic cloning

The conventional term «therapeutic cloning» is misleading, inasmuch as the cloned embryo or the resultant individual is not itself the beneficiary of the therapeutic measure. While the cloning procedure is indeed performed with therapeutic intent, this relates to a different patient. An embryo cloned from the nucleus of a cell taken from the patient is the source of embryonic stem cells from which immunocompatible, transplantable tissue is to be cultured. Although the terms «research cloning» and «non-reproductive cloning» have been proposed as alternatives, «therapeutic cloning» is used by the NEK-CNE, as this term is now well established. The considerations of the NEK-CNE cover the following points:

1. Therapeutic cloning needs to be considered in two distinct scenarios – with natural and with artificial oocytes. In both cases, the primary ethical issue is raised by the fact that an embryo-like entity, possibly exhibiting a certain capacity for development, is to be artificially created for research purposes. This represents complete instrumentalization of the cloned embryo for third-party purposes. If artificial oocytes were used, a special situation would arise: firstly, it would rule out the objection that a woman is being instrumentalized as a donor or supplier of oocytes. Secondly, the cloned embryo would be unsuitable for the establishment of a pregnancy not only on account of the cell nuclear replacement but also because of the artificial origins of the oocytes.
2. However, the NEK-CNE is not persuaded by the argument that somatic cell nuclear transfer (SCNT) is in itself morally outrageous and automatically renders the method of therapeutic cloning ethically untenable. This argument would be comprehensible if it were assumed that a person is created when fertilization occurs – the production of an embryo by SCNT would then have to be regarded as the production of a person. This would have to remain prohibited, as it cannot be permissible for people to be produced merely as raw material for the purposes of third parties. However, the NEK-CNE has not adopted this conception of human dignity. Rather, the majority of Commission members share the view that, while a certain dignity attaches to the embryo from the outset, it develops gradually. In the view of the Commission, reproductive cloning is to be prohibited not on the grounds that it involves the method of SCNT, but for a number of other ethical reasons (cf. NEK-CNE Opinion no. 4/2003: «Reproductive human cloning»).
3. An argument relating to legal practice needs to be discussed: is it even possible to distinguish therapeutic from reproductive cloning in practice? Can one prohibit embryos produced by SCNT from being transferred into a woman's uterus, or is it foreseeable that therapeutic cloning would lead to the implementation of reproductive cloning? In response, it has been argued that if an embryo is to be transferred, a woman must be prepared to carry it to term, and that the embryo transfer and completion of a pregnancy constitute additional acts. These acts are in principle objectively distinguishable and ascertainable, and they can therefore be covered by criminal law provisions and remain prohibited.
4. Another possible objection is that therapeutic cloning would favour those who have the necessary resources at their disposal (money, their own oocytes, a favourable environment,

etc.). From an ethical viewpoint, however, it would be difficult to reject therapeutic cloning on the grounds that it would scarcely be possible for all the patients requiring treatment to benefit from a procedure of this kind. Organ donation remains permissible despite the fact that some patients who need an organ are unable to find a suitable donor.

5. On pragmatic grounds, a regime based on regulatory controls could be preferred to a ban on therapeutic cloning. If therapeutic cloning is permitted in other countries, prohibition would lead to problems concerning the coexistence of two different regimes.
6. In the assessment of therapeutic cloning, the fact that cloned embryos have a reduced developmental potential as a result of faulty reprogramming of the transferred cell nucleus should be taken into account, but it cannot in itself justify a decision to permit the procedure. It cannot be denied that the cloned embryo has a capacity for development, even if it is foreseeable that the procedure will lead to serious developmental disorders and damage to health. In theory, it would be possible for cloned embryos to be endowed with a mutation that would prevent them from developing beyond the blastocyst stage. However, the NEK-CNE has doubts about this strategy, as it would expose patients to additional risks merely in order to address, in an obvious manner, a single ethical objection divorced from its context.
7. Under Art. 119 Para. 2c of the Federal Constitution (BV), it is prohibited to use the techniques of medically assisted reproduction in order to carry out embryo research. The underlying principle is that an embryo is only to be created for purposes relating to its own life and development. If the product of SCNT is recognized as an embryo, therapeutic cloning violates the principle that embryos are not to be created for research purposes. Technically, however, the provisions of BV Art. 119 Para. 2c would only be breached if at the same time cloning (SCNT) were recognized as a technique of medically assisted reproduction. But this is implausible, given the general ban on reproductive cloning that is enshrined in the same article of the Constitution. Thus, from the perspective of constitutional law, a case could be made for permitting therapeutic cloning, provided that the general ban on cloning were to be more precisely defined as a ban on all kinds of reproductive cloning. The context in which BV Art. 119 was drafted suggests that it was not in fact intended to go beyond a general ban on reproductive cloning. However, for the Commission, what seems more important than the question of whether therapeutic cloning is technically compatible with the Constitution, is the question of whether it conflicts with the moral principles of embryo protection. Within the Commission, the answers given to the question of whether a cloned embryo is morally equivalent to a naturally conceived embryo are neither uniform nor definitive – the need for ethical clarification would appear to be too great. The lower likelihood of normal development does not in itself provide sufficiently convincing grounds for treating the cloned embryo differently, nor does the intention to create an embryo for the purposes of stem cell production, or the ethical and legal prohibition on further development of the cloned embryo. A difference in the method of creation cannot justify unequal moral treatment of the products of the various methods. Equally unconvincing are efforts to deny that an embryo created by SCNT has a claim to protection by classifying it as an «artefact». For there are other cases where reproductive medicine also intervenes to a greater or lesser extent in the natural processes whereby embryos are created, thus rendering them, in some sense, «artefacts», without their entitlement to protection being lost as a result.

Within the NEK-CNE, there is no consensus on the question of a general ban on therapeutic cloning. The following two opposing positions are adopted:

Position A: A large majority of the Commission can see no fundamental ethical grounds that would definitively support or rule out the legalization of therapeutic cloning. Nonetheless, it

does not at present see any reason or any urgent need to lift the existing ban on therapeutic cloning and recommends that it should be maintained.

The reasons for this position are as follows:
(1) There is a need for clarification of the ethical implications of SCNT technology, especially with regard to the claim to protection of the SCNT embryo.
(2) In the current state of biomedical research, it is not clear whether therapeutic cloning will ever represent the only effective treatment option for certain serious diseases. This means that there are no convincing ethical grounds for permitting therapeutic cloning.

If the procedure were to be permitted, the following conditions, in particular, would have to be met:
(1) The protection of women as oocyte donors would have to be guaranteed.
(2) The research objective would have to be of major significance for human health, if there were no direct therapeutic reasons for using the procedure.
(3) It would also have to be ensured that the cloned embryo cannot develop beyond the blastocyst stage.

Position B: A minority of the Commission rejects therapeutic cloning for fundamental reasons. The following considerations are decisive: Firstly, there could be expected to be a great demand for oocytes, which could scarcely be readily met by voluntary donations, without any «moral pressure» being exerted on potential donors. Secondly, the production of artificial oocytes is also questionable, as these could be subjected to selection and/or genetic manipulation. If they were then fertilized and implanted in the body of a woman (despite such a procedure being prohibited), this would resemble the «designer baby» model. However, the main argument against therapeutic cloning is that it could lead, via a slippery slope, to reproductive cloning. This concern would persist even if the question of the demand for oocytes were resolved. Experience has shown that everything that can be done will be done by researchers. Ethically irresponsible developments should therefore be stopped while this is still possible.

Special problems are raised by interspecies clones (or «SCNT hybrids»), which can be created by inserting a human cell nucleus into an animal oocyte, or an animal cell nucleus into a human oocyte. This scenario has been discussed, for example, in connection with the production of embryonic stem cells from blastocysts, but it could also be considered for experiments of other kinds. On this question, the conclusions of the NEK-CNE are as follows:

a) The Commission essentially regards the analogy with therapeutic cloning as offering a plausible model for the regulation of SCNT hybrids.
b) The majority of the Commission (cf. Position A above) sees no fundamental ethical objections to the creation of hybrids. However, it also notes the existence of normative/ethical uncertainties comparable to those associated with therapeutic cloning. It should not be possible to circumvent a ban on therapeutic cloning by using animal oocytes. It would be ethically highly questionable if SCNT hybrids, used to produce autologous stem cells for a patient, were only created in order to circumvent a ban on therapeutic cloning, with patients being exposed to increased risks as a result.
c) As the properties of these constructs have not been elucidated, the NEK-CNE recommends that their use should not be permitted. The same approach should be adopted as for therapeutic cloning, i.e. legalization should not be contemplated at present.

3.3.3 Parthenogenesis and androgenesis

It has sometimes been suggested that stem cells could be obtained from embryos that have developed merely from the division of oocytes (i.e. without fertilization), rather than embryos produced by fertilization being used for this purpose. Through technical manipulations, such entities could be induced to develop over a number of days as far as the blastocyst stage. At present, however, they are believed to be unlikely to have the capacity for further development, even with artificial stimulation. In theory, this biotechnological strategy could be used not only for stem cell procurement but also for other research purposes or applications. The parthenogenetic embryos produced by this technique are genetically female. If one wishes to produce genetically male embryonic entities, two male pronuclei can be inserted into a previously enucleated oocyte (androgenesis). Legal definitions of the term «embryo» are often based on the idea of fertilization as the fusion of a female and a male gamete; by producing parthenogenetic embryos or using androgenesis, it would thus be possible to circumvent the legal provisions regulating the handling of embryos. The following ethical points were considered by the NEK-CNE:

1. The absence of a capacity for further development on the part of the entities concerned can be considered to be the main ethical argument supporting the legalization of parthenogenesis and androgenesis. If they lack the biological potential for development, they also lack the decisive property on which the embryo's moral claim to protection rests – the capacity for development. This type of moral claim to protection would thus not be applicable to parthenogenetic embryos.
2. The NEK-CNE has identified two arguments against the creation of parthenogenetic embryos for research purposes:
   a. Firstly, parthenogenesis is dependent on the availability of oocytes. If one rejects oocyte donation in general, or takes the view that human oocytes should not be available in laboratories for research purposes, parthenogenesis would also have to be rejected. Oocyte donation is problematic because it is an invasive procedure which may pose risks for donors. However, this concern would not rule out the use of oocytes produced in vitro from stem cell cultures. It would also be less pertinent if the oocytes in question became available, for example, as a result of surgical removal of a patient's ovaries and were donated for research purposes by the woman concerned. The objection would likewise be less relevant in the case of surplus oocytes, no longer required after a successful IVF procedure and donated to research by the woman in question. In all of these cases, however, the consent procedure would have to be subject to stringent requirements, because if a woman is already dependent on medical assistance, her ability to decide freely when faced with a request for oocyte donation may be restricted.
   b. The second argument relates, as mentioned above, to embryo protection: the term «parthenote», which is frequently used in the debate, suggests a different moral status from that of an embryo. As the NEK-CNE does not wish to circumvent the question of the claim to protection by terminological means (thereby prejudging the issue of moral status), it prefers to speak of «parthenogenetic embryos».
3. A point that to date has been of a more theoretical nature also needs to be discussed: could parthenogenesis perhaps also be used for reproductive purposes in the future? If reproductive cloning is prohibited, then the production of parthenogenetic embryos for reproductive purposes would logically also have to be prohibited. From an ethical viewpoint, there is no difference between parthenogenesis for purposes of reproduction and reproductive cloning. The only difference lies in their relative biological plausibility: while parthenogenetic embryos have never been observed to develop beyond the blastocyst stage, cloned embryos have – at least in animal experiments – been shown to be capable of further development.

4. A special situation arises if a patient is to be treated with cells or tissue deriving from parthenogenetic embryos from autologous oocytes. In this case, there is a close analogy with autologous bone marrow transplantation, although it involves the intermediate step of cell division. The case is also comparable to therapeutic cloning with autologous oocytes. For the regulation of medical research, this scenario is relevant if therapeutic efforts are undertaken in the context of a research protocol. Even if the intention is purely to treat a patient, however, the procedure also requires regulation since it involves the production, for the benefit of a third party, and the destruction of embryonic human life.
5. For the purposes of legal and ethical appraisal, it is irrelevant whether a parthenogenetic embryo is diploid or haploid since it cannot be assumed to have the capacity to develop beyond the blastocyst stage.
6. As regards the ethical assessment of the parthenogenetic embryo's claim to protection, an analogy exists with therapeutic cloning. Both cases involve scientific and ethical uncertainties, which were taken into consideration in the assessment.

Within the NEK-CNE, there is no consensus on the question of whether parthenogenesis should be permitted. The following two opposing positions enjoy roughly equal levels of support:

Position A: Some members of the NEK-CNE have no fundamental ethical objections to the production of parthenogenetic embryos for purposes of research. This is because parthenogenetic embryos appear to lack the potential for further development – complex technical support is required even for the attainment of the blastocyst stage. It is therefore possible for their production and destruction to be weighed up against therapeutic benefits. However, in addition to the general requirements (see above), it would be necessary to ensure that:

(1) women are not subjected to any additional ovarian stimulation for this purpose;
(2) no pressure is exerted on women to donate oocytes that are no longer required;
(3) the research objective is recognized to be of major significance;
(4) development does not proceed beyond the blastocyst stage; and
(5) after investigation or the extraction of stem cells, the embryo is destroyed.

This part of the NEK-CNE recommends that legislators should review the existing ban in Switzerland on the production and use of parthenogenetic embryos for research purposes. At present, however, it recommends that the ban should be maintained.

Position B: For a second group within the NEK-CNE, the ban on the production and use of parthenogenetic embryos for research purposes is justified and should remain intact. This position is adopted, firstly, on account of the risks associated with oocyte donation. The development of the procedure, in itself, would give rise to a great demand for oocytes, subjecting potential donors to moral pressure. Secondly, the use of artificial oocytes would also be questionable, given the possibility of selection and/or deliberate manipulation in the production of parthenogenetic embryos. If parthenogenetic embryos were used for purposes of transplantation, this would additionally represent the instrumentalization of human embryos, which is either considered to be fundamentally unacceptable or – by some members of the Commission – is ruled out in view of the need for ethical and scientific clarification.

3.3.4 Chimeras and hybrids

A chimera is an organism composed of cells from different individuals. Different moral questions arise depending on whether interspecies or intraspecies chimeras are considered, what

species are involved and what stage of development the two individuals have attained. The various questions are assessed individually below. In this publication, the Commission only considers cases involving the use of human embryonic cells or embryos. At present, the creation of human/animal chimeras is mainly contemplated in research that is concerned with studying the developmental potential of stem cells. In such cases, human embryonic stem cells or even certain types of adult stem cells are introduced, for example, into mouse blastocysts. Subsequent development is observed, and experimental studies are carried out to determine which mouse tissues or organs include human cells. In the Commission's assessment, the following points were considered:

1. A strong moral intuition argues against the mingling of different species. The creation of human/animal mixtures is intuitively felt to be shocking. However, a closer examination of what underlies these intuitions shows that they are not in themselves sufficient to justify a general and absolute ban on the mixing of species. It should be noted that:
   - Very few people are unequivocally opposed to the introduction of a single human gene into an animal or, conversely, to the use of a therapeutically effective gene of animal origin in human somatic gene therapy.
   - Moreover, many people would barely object if it transpired that a single animal cell had established itself in their body. (In actual fact, everyone harbours numerous foreign organisms that live symbiotically inside the human body without damaging the host's health or sense of identity.) Conversely, the implanting of a single human cell in an animal would scarcely be construed as humanization of the creature concerned.
   - In addition, the use of adult animal tissue in humans for therapeutic purposes is already accepted (e.g. animal heart valves).

   Additional metaphysical or religious arguments are therefore required if a general and absolute prohibition on crossing species boundaries is to be established. The NEK-CNE was not persuaded by the view that the species boundary is universally and categorically inviolable, and that it is therefore impermissible to mix cells from different species. The situation is rather different, however, if human cells form structures, parts of organs or entire organs in an animal organism. If human cells (e.g. in a monkey embryo) assume control over the development of an animal, and human features or human characteristics emerge in the creature, the bounds of what is tolerable (on the grounds of protection of animal and human dignity) have been exceeded. The possibility of such chimeras developing a rudimentary form of human sensibility – or even early forms of human consciousness – cannot be ruled out. The Commission takes this concern seriously.
2. The question thus arises of whether it is possible to restrict chimera experiments in such a way as to prevent the development of human organ parts or structures in an animal organism. Another question that needs to be considered is whether it would be possible to limit the period of development of the chimeric embryo to a certain prenatal stage.

A special kind of embryonic chimera is produced by the combination of two human embryos (human intraspecies chimera). Chimerism of this kind may also occur spontaneously, involving either twins or (very rarely) embryos deriving from two different fathers. From a normative viewpoint, a distinction needs to be drawn between (1) experiments designed to yield scientific knowledge and (2) the creation of chimeric embryos with therapeutic intent.

1. **Intraspecies chimeras for research purposes:** experimental studies on human intraspecies chimeras could facilitate the investigation of mechanisms of immunocompatibility. Knowledge of the development of immunological compatibility and incompatibility is of major significance in increasing the safety of cell, tissue and organ transplants, also in the field of stem

cell medicine. In the experimental production of embryonic chimeras, key issues of embryo protection arise. However, the procedure would not necessarily involve the creation of embryos for research purposes – the embryos used to produce chimeras could also have been created for the purpose of establishing a pregnancy and have been left over. The manipulation may alter the pace of individual steps in embryonic development, e.g. gastrulation.

2. **Intraspecies chimeras for therapeutic purposes:** in this case, healthy cells from one embryo would be implanted in a second embryo, for example, in order to correct a metabolic defect. The embryo receiving a transplant of embryonic cells or tissue is thus itself the subject of a therapeutic intervention. The presence of the defect would, however, have to be detected in advance by means of embryo biopsy. In certain cases – e.g. dominant genetic disorders – the defect would be predictable on the basis of the mode of inheritance.

The term «hybrid», lastly, refers to the product of the fusion of gametes of different species (interspecies fertilization) or an embryo produced by transferring the nucleus of a human cell into an enucleated animal oocyte. There have been no reports of human gametes (of either sex) being successfully combined with gametes of any non-human animal species. While it is possible to use animal gametes to study the acrosome reaction of human germ cells (whereby penetration of the oocyte by more than one spermatozoon is prevented), this reaction occurs on the surface of the oocyte before a single spermatozoon has penetrated the egg cell membrane. Karyogamy and further development by natural means appear to be impossible. Although it is conceivable that a spermatozoon of a different species could be introduced into an oocyte by technical manipulation, karyogamy and further development would be blocked by differences in chromosome type and number.

A hybrid created by nuclear transfer, from its inception to the blastocyst stage, is difficult to classify biologically. It is to be regarded neither as a human embryo (because the mitochondria and ooplasm are of animal origin) nor as an animal embryo (because the genes are human and the animal proteins disappear over time). Biologically, it cannot be precisely predicted what such hybrids will develop into. However, since the question of moral status cannot be answered solely on the basis of biological characteristics, it remains the subject of an ethical assessment. The recommendations of the NEK-CNE on this question are given above in the section on «therapeutic cloning» (see p. 12).

Overall, the issue of chimeras/hybrids involves a number of scenarios, with different views being taken in each case. With regard to interspecies chimeras for research purposes, the following opposing positions are adopted within the NEK-CNE:

Position A: A large majority of the NEK-CNE has grave doubts about the production of interspecies chimeras. If one wishes to investigate, for example, which parts of the mouse body exhibit the presence of human stem cells after development, and whether they are capable of forming different types of tissue, the aim of the experiment is to promote the development of human structures in an animal organism. What is of interest from the researcher's perspective is the development of tissue and organ structures with the involvement of human cells, not the absence of such structures. For a majority of the Commission, it would therefore appear to be a more convincing strategy to prohibit the production of chimeras resulting from the combination of human stem cells with animal embryos than to seek to define limits – an undertaking which from the outset seems unlikely to succeed. However, it would have to be ensured that the prohibition was not formulated in such a way as to exclude animal/human mixing in all cases, since this would also rule out, for example, the use of animal heart valves or cellular xenotransplantation. The prohibition would have to be of limited scope, covering the combination of human cells with animal embryos, or parts thereof with the capacity for

development (and vice versa). The introduction of human cells into developed animal organisms is also to be ruled out for the same reason, although this does not concern the field of embryo research in the narrow sense.

Position B: A minority of the NEK-CNE considers restricted legalization of chimera experiments to be a possibility, arguing that limits could be defined for permissible chimera experiments. It would have to be ensured that (1) development is terminated before the end of organogenesis and (2) further development would only be permitted if it is certain that development would not be controlled, even in part, by the implanted cells. Provided that experiments are conducted within these limits, no human interests or rights are affected.

With regard to intraspecies chimeras, the NEK-CNE distinguishes between production for purposes of research and for therapeutic purposes. In the former case, the following opposing positions are adopted:

Position A: One half of the NEK-CNE proposes that the production of intraspecies chimeras for research purposes should be prohibited, on the grounds that complete instrumentalization of an embryo for research purposes is forbidden. The embryo would not merely, as in the case of stem cell harvesting, be broken down into individual cells at an early stage in its development, before the stem cells have undergone any differentiation; rather, its development would be allowed to proceed for a time under artificial conditions, to enable studies to be carried out on it. The procedure is to be regarded as the production of embryos for research purposes even if in the case of the two original embryos oocyte fertilization was not performed for research purposes.

Position B: The other half of the NEK-CNE takes the view that the procedure could be permitted under certain explicitly formulated conditions. As long as the experiments are conducted with surplus IVF embryos, within the meaning of the Stem Cell Research Act, they represent just one of the many research scenarios that can be envisaged with these embryos. One crucial condition would be that growth would only be permitted until the beginning of organogenesis (i.e. until the stage that is attained, with natural development, about 2 weeks after fertilization) and the embryo would then be destroyed. A further condition would be that the embryos used had not been fertilized for research purposes, but had been created for the purpose of establishing a pregnancy and had been left over, for independent reasons, from an IVF procedure. This part of the Commission sees no ethical grounds for an absolute ban on experimentation with human embryos. The experimental production of chimeras is merely one of a number of possible methods of investigation.

With regard to the production of intraspecies chimeras for therapeutic purposes, the following positions are adopted:

Position A: One half of the NEK-CNE proposes that the production of intraspecies chimeras in the context of therapeutic efforts should be prohibited. This procedure envisages the treatment of one embryo using part of a second embryo, which serves as a source of cells or tissue and is destroyed in the process. In addition, it is feared that there may be risks of developmental malformations. There could also be a tendency to use more than merely minimal parts of the second embryo. The developing human being would thus originate from several people, breaching the rule that biological parentage is restricted to two people. The deliberate violation of this rule can be considered to be ethically relevant, even though in very rare cases triple biological parentage may also occur spontaneously.

Position B: The other half of the NEK-CNE proposes that this question should be provisionally left unresolved, rather than being resolved by means of a ban. For these members of the Commission, the production of intraspecies chimeras for therapeutic purposes in humans could be ethically acceptable if a series of conditions were formulated and complied with. It would need to be a requirement that the treated embryo should clearly maintain control over the processes of development, and that the contributions of the transplanted embryo parts should remain unspecific. In addition, it would have to be possible to rule out risks of malformations. Plans for embryo therapy of this kind could only be approved on the basis of specific projects, and authorization would have to be carefully considered with particular attention to risks and side effects – and, if there were any doubt, withheld. This is a special type of situation, in which the possible success of treatment is to be weighed up against the risks and side effects without reference to an existing patient. At the time of this deliberation, the patient does not yet exist and would only be created with a view to the therapeutic effort in question. This act of creation can also fail to take place without the (non-existent) patient suffering. For this reason, at the time such treatment is planned, there is no moral duty of care, or «therapeutic imperative», which otherwise provides an ethical motivation for medical treatment and care, and could also justify the acceptance of risks and side effects.

With regard to the production of hybrids, the following positions are adopted by members of the NEK-CNE:

Position A: For reasons of consistency with the position on reproductive parthenogenesis, which is likewise biologically implausible, and from a deep-seated intuition opposing the fusion of human and animal gametes, most members of the NEK-CNE propose that the fusion of human and animal gametes should be prohibited.

Position B: For a minority of the Commission, it is at most conceivable that this procedure, which is a matter of speculation, could be permitted subject to certain restrictions, as long as it were ensured that the hybrid embryos produced for research purposes could not develop beyond the beginning of organogenesis, and that they would be destroyed at this point. A ban on the use of procedures involving hybrids for reproductive purposes is, however, also supported by this part of the Commission.

Chapter IV: Ex vivo embryos and fetuses

4.3 Considerations and recommendations of the NEK-CNE

The NEK-CNE draws a fundamental distinction between research that places the embryo's development at risk, renders future development impossible or destroys the embryo (invasive or destructive embryo research) and research of an observational, non-invasive nature, which involves no or only minimal risk to the embryo and is compatible with its development into a fetus and child (non-invasive research). A third category is represented by efforts to treat the embryo in vitro (therapeutic research/efforts). This chapter is concerned with research that falls into the first of these categories. Ethical questions associated with therapeutic cloning and stem cell research have already been discussed in detail in the previous chapter. Finally, the reader is referred to NEK-CNE Opinion no. 3/2002 for a detailed assessment of stem cell research issues.

With regard to investigations that jeopardize or prevent the embryo's healthy development, three questions need to be answered. Firstly, for which embryos – if any – should such investigations be permissible? Secondly, what types of research project should be permissible? And thirdly, within what time frame, or up to what developmental stage, should embryo research be permissible?

The only embryos that are to be considered eligible for research that poses risks to their healthy development, or is incompatible with their further development, are those not intended to be used in establishing a pregnancy. These may be surplus IVF embryos, within the meaning of the Stem Cell Research Act, or embryos that are not suitable for reproductive use in view of suspected or diagnosed abnormalities. On the latter point, the following considerations are relevant:

- The only (invasive) method of investigating embryos intended for reproductive use (within a parental project) that is currently under discussion is preimplantation genetic diagnosis by embryo biopsy. This procedure is designed to provide information on the genetic status of the embryo before it is transferred to the uterus, without, as far as possible, involving any risks for the embryo. Preimplantation genetic diagnosis (PGD) has been discussed in detail by the NEK-CNE elsewhere (cf. NEK-CNE Opinion no. 10/2005). It is regulated by the Reproductive Medicine Act (FmedG) and is at present completely prohibited in Switzerland. If PGD were in future to be permitted within certain limits, it would only need to be regulated by the Human Research Act insofar as it is to be carried out for research purposes. The use of embryo biopsy for research purposes may be associated with and accompany the performance of such a biopsy for reproductive purposes. However, this constitutes a special case, inasmuch as the intervention placing the embryo at risk is diagnostically motivated in the context of a reproductive project and must also be justified on this basis, rather than by the research objective. Research would as it were merely be taking advantage of the opportunity, arising from an independently planned PGD procedure, to study embryonic cells. But if an embryo biopsy is motivated by research purposes, it represents invasive research, placing the embryo at risk, and would be covered by the relevant provisions of the Human Research Act.
- A special situation arises if a diagnostically motivated PGD procedure within a parental project yields abnormal findings that would make reproductive use inadvisable, and if the embryo is then not transferred to the woman's uterus. The embryo in question thus

becomes in a special sense supernumerary, but at the same time could be of particular interest for research (e.g. for studies of early developmental steps directly associated with the diagnosed disorder).
- A similar situation arises if, during an IVF procedure, an embryo exhibiting abnormal morphology is visually screened out and judged to be unsuitable for implantation on account of a suspected developmental disorder. Such situations also occur within the existing legal regime, under which PGD is prohibited.

A wide variety of requirements could be specified for research projects, ranging from a complete ban, irrespective of the purpose of research, to a complete lack of restrictions. Intermediate positions would permit only those research projects that benefit other IVF embryos (optimization of methods of reproductive medicine), those that promote the development of treatment methods (therapeutic goals), or those deemed to have «high-priority» goals. The Commission favours the priority criterion as it does not prejudge issues in a manner that would be difficult to justify. A requirement common to all of these approaches is that projects can only be contemplated if informed consent has been freely given by the couple concerned.

The period within which in vitro embryo research is permissible should be restricted to the blastocyst stage. An extension of the time frame – e.g. to 14 days, as in certain other countries – is not recommended. In its recommendations on stem cell research, the Commission itself proposed a limit based on the developmental stage «blastocyst», which roughly corresponds to the 6-day limit specified in the Stem Cell Research Act. For the Commission, the ethically decisive criterion is the developmental stage, rather than the number of days.

In connection with **termination of pregnancy**, the following fundamental principles apply:

1) An important ethical principle for the conduct of research on embryos and fetuses during or after pregnancy is that the decision concerning a termination and the procedure itself are to be strictly independent of the question of whether the aborted fetus is to be used for research purposes. This question may only be raised after the decision to terminate a pregnancy has been made. It needs to be borne in mind that in the period preceding the termination the mother can in principle still change her mind. This option must not be closed off by research.
2) After a medically indicated termination of pregnancy, the woman's consent is required for any investigation of the embryonic/fetal tissue designed to check the results of prenatal diagnosis or to improve diagnostic methods. While investigations of this kind may serve quality control purposes rather than being part of a formal research project, they should be subject to the same conditions as research projects.
3) There can be no ethical justification for establishing or terminating a pregnancy with the intention of creating opportunities or procuring materials for research.
4) The two activities must also be clearly separated in terms of personnel and physical location. The people involved in the termination of a pregnancy or responsible for the woman's clinical care should not be involved in the related research.
5) Neither the mother nor people who could influence her decision should be offered incentives (of a financial or non-financial nature) providing encouragement to terminate a pregnancy, to consent to research, or to permit the use of embryonic/fetal tissue.

For **research** on abortuses or on embryos that are to be aborted, the following fundamental principles apply:

1) In this situation, by definition, any research is «for the benefit of third parties» since benefits to the embryo/fetus that is the subject of the research cannot be invoked to justify such interventions if the embryo/fetus is to be aborted.
2) Research must not harm the mother or fetus. In addition, interventions must not involve pain either for the embryo/fetus or for the mother.
3) Invasive research (e.g. removal of fetal tissue) may only be carried out if it coincides with the killing of the fetus and does not impose any additional burdens on the woman or fetus.
4) In the interests of the woman and of the fetus, the timing of a termination is not to be altered on account of research interests.
5) In principle, it is not permissible to take research interests into consideration when choosing the method of abortion. Exceptions may be made if they are acceptable to the woman and do not affect her health. The method selected must primarily be that which is considered most gentle for the woman (and the fetus).
6) Ethically reprehensible research goals are theoretically conceivable (e.g. the development of discriminatory practices or techniques for personality manipulation). However, in assessing the ethical integrity of research goals, the same ethical considerations are required as for other fields of research. There are no special criteria for the ethical unacceptability of the objectives of research on abortuses which are not applicable to research in general.

Assuming that a gradualist position is adopted, the moral status of an abortus depends on the age of the fetus. In the case of fetuses (from about the 15th week of pregnancy) that can survive for a time after leaving the womb, the moral claim to protection is most significantly affected by whether the fetus is alive or has already died. The question of whether invasive research may be carried out in the period preceding the death of the fetus is to be answered in the negative. But the utmost restraint is also to be exercised regarding non-invasive research, out of consideration for the mother's feelings, but also for reasons of respect. With regard to the criteria for death, the following points should be noted:

1) In the case of abortuses, the cessation of heartbeat and respiration is taken to indicate that death has occurred. For a definition of clinical death, the reader is referred to the guidelines published in August 2005 by the Swiss Academy of Medical Sciences.[1]
2) An embryo/fetus is not to be kept alive artificially in order to make it possible for experiments or investigations to be carried out. If it must die, the embryo/fetus should have the «right» to die quickly and painlessly. This is dictated by a sense of respect – i.e. appropriate consideration.

As regards the handling of biological material deriving from abortuses, the same principles are applicable as for the handling of biological material from deceased patients.

Within the NEK-CNE, the following three positions are adopted, with varying levels of support, on the regulation of invasive embryo research:

Position A: A small minority of the Commission recommends a ban on research that places the embryo at risk or is destructive. The proposals take two forms: either a complete ban on all embryo research or a limited ban, prohibiting research on embryos exhibiting no suspected or diagnosed abnormalities. The justification offered for a complete ban on research (first proposal) is as follows: the destruction of embryos or their exposure to risks or harm for purposes not connected with the promotion of their own health represents the instrumentalization of nascent human life and is therefore fundamentally incompatible with the dignity of the embryo. The call for a limited ban on research (second proposal) is based on the concern that

[1] This publication can be downloaded from the website: www.samw.ch

a competition for resources may arise between the use of surplus embryos for stem cell harvesting and their use for embryo research. This competition could give rise to an ever-increasing demand for surplus embryos, possibly strengthening calls for the artificial production of embryos. Such competition could be eased by only permitting research to be carried out on embryos classified as abnormal on the basis of a visual assessment (this position rejects diagnostic embryo biopsy).

Position B: The great majority of Commission members recommend that projects involving invasive research should be permitted if the following conditions are met:

a) The embryo is either a surplus embryo, within the meaning of the Stem Cell Research Act, or exhibits suspected or confirmed abnormalities that preclude embryo transfer and the establishment of a pregnancy.
b) The embryo is only allowed to develop to the blastocyst stage.
c) The research project must have high-priority goals.

This majority is persuaded by the analogy with the regulation of the harvesting of embryonic stem cells from surplus embryos. Stem cell procurement can be regarded as a special type of experimental intervention, which from an ethical viewpoint is not to be treated any differently from other methods of investigating the characteristics of such embryos. However, it is also a requirement here (as discussed in detail in NEK-CNE Opinion no. 2/2003 on embryonic stem cell research) that research is only permitted in the case of embryos that have been left over for independent reasons and would not otherwise be allowed to develop further or be used to establish a pregnancy. In this situation, protection of the embryo's life is not possible. Legislators should be aware that if these provisions were to apply, competition could arise between the various uses to which the small number of available embryos could be put (e.g. stem cell procurement and other research projects). Distribution and allocation issues would arise, which would have to be dealt with transparently and equitably.

Position C: For another small minority of the Commission, the question arises whether it would also be permissible (contrary to the existing regulations) for embryos also to be created for research purposes; this would ensure that there was no competition with the use of embryos for stem cell procurement. The justification offered for this minority view is that the obligation to protect the early embryo is not so great as to rule out any consideration of the potential advantages. In addition to the benefits for research, these lie in the fact that donors' consent would be more unequivocal if the project from the outset did not involve parental aspirations. Donors would only consent to the creation of an embryo to be used for research purposes if they found this prospect emotionally and morally acceptable.

The set of questions submitted by the Swiss Federal Office of Public Health (SFOPH) included a series of specific queries in connection with invasive embryo research. The Commission's responses are as follows:

What view is to be taken of research involving material (cells and cellular substances) that is yielded by diagnostic procedures?
As in the case of research involving in vivo embryos and fetuses, the most important point is to ensure, through appropriate regulations, that the decision to carry out the diagnostic procedure is not influenced by the research objectives. A couple's consent to a research project may only be sought once the decision to carry out the diagnostic procedure has already been taken – for reasons independent of the research project.

What is the moral status of surplus embryos? Does their moral status differ from that of embryos required for reproductive purposes?
The majority of the NEK-CNE assumes that we humans owe ethical respect and consideration to all ex vivo embryos, whether they are classified as surplus or not. Surplus embryos therefore do not differ in their moral status. However, a different situation arises in view of the consequences that an intervention for research purposes has for the nascent child.

On what grounds is stem cell procurement to be differentiated ethically from embryo research for other purposes?
For the majority of the Commission, there is no reason for legislation to differentiate between stem cell procurement and embryo research for other purposes. However, the minority that adopts Position 1 above justifies a distinction as follows: In stem cell procurement, the embryo is destroyed, with freedom of research being accorded greater value than the embryo, and human life being instrumentalized in the interests of third parties. The same applies to embryo research. However, while stem cell procurement is an act performed on a single occasion, experiments and studies are carried out on isolated and cultured cells. If the experimental procedures are performed on the embryo itself, a different situation arises for the embryo concerned, depending on the nature of the research protocol.

From an ethical viewpoint, is there any difference between a research project designed to improve procurement methods and a research project involving surplus embryos?
Assuming that «procurement methods» refers to methods for the procurement of embryonic stem cells, no ethically relevant features are apparent that would justify treating research projects of this kind differently from projects designed to yield knowledge in other areas.

What criteria do research goals have to meet in order for them to be considered of sufficiently high priority to justify destructive embryo research?
If regulations permit experiments that place embryos at risk or are of a destructive nature, making them conditional on «high-priority research goals», the question arises whether these general provisions should be specified in greater detail in the law itself. It would be possible to define high-priority goals in terms of benefits for other in vitro embryos, or in terms of potential benefits for patients afflicted by certain diseases. However, it is scarcely possible to define general rules as to whether a concrete research protocol meets such criteria. Deliberations will always be required in specific cases. In the view of the Commission, the regulations should assign responsibility for the task of interpreting «high-priority goals» in individual cases to the cantonal ethics committees for clinical research.

Does an embryo/fetus that is to be aborted have a different moral status?
No. Since moral status is intrinsically defined, it is independent of the decision as to whether an abortion is to be performed. An embryo or fetus that is to be aborted has the same claim to protection as one that is allowed to develop further. Accordingly, the same criteria should be used as are applicable for in vivo embryos/fetuses in general. The fact that the embryo/fetus is subsequently to be aborted does not mean that it may be subjected or «sacrificed» to research beforehand.

Chapter V: In vivo embryos and fetuses

5.3 Considerations and recommendations of the NEK-CNE

Research on human embryos and fetuses in vitro and in vivo raises ethical problems because it may involve adverse consequences both for the embryos and fetuses studied and for the mother. As well as yielding results that are important for research (e.g. measurement data), interventions may have further consequences (e.g. a risk of miscarriage, knowledge of a predisposition to disease). Such consequences are unavoidable, even if the practices adopted are as gentle as possible, but in some cases they may be undesirable – either for the fetus (which may already have a degree of sentience), the developing child, or the woman, or for the pregnancy, mother-child relationship or family. In such situations, therefore, research studies always involve possible conflicts of interest, which need to be carefully examined in specific cases. Particular aspects and criteria deemed relevant by the NEK-CNE are presented in detail below.

The following general **ethical principles** apply to research on in vivo embryos/fetuses. These conditions are also applicable to ex vivo studies that could be carried out after a termination of pregnancy or a miscarriage.

1) The interests of the mother, the father and the family, but also the sensations of the fetus and the subsequent interests of the developing child must be appropriately protected vis-à-vis research interests. To this end, certain research projects that are inevitably detrimental to these interests are to be ruled out. Others are to be carefully planned so as to avoid conflicts of interest.
2) In all cases, research interventions may only be performed if the woman concerned has freely consented, having received comprehensible verbal and written information on the procedure. In general, consent is to be given in writing. The woman must have the right to withdraw her consent at any time without giving reasons. It is desirable that the parents should arrive at a joint decision, supported by both parties. If no agreement can be reached, the decision rests with the pregnant woman.
3) No member of the nursing/medical team may be required to participate in research projects involving embryos or fetuses against the dictates of his or her conscience. However, the right not to participate (refusal) does not extend to the provision of care for the patient before or after such a procedure is carried out. Appropriate precautions must be taken to ensure that when tissues, cells or information are passed on, the couple's anonymity and the confidentiality of data are guaranteed.
4) All research projects, including those that involve the development of innovative treatments (such as today's in utero surgery, stem cell transplantation, in utero gene therapy, etc.), must have been assessed in advance by the competent cantonal ethics committee, which should ensure that:

    1. the rights, dignity and health of the woman concerned and also, as appropriate, of the embryo or fetus are protected;
    2. the project is scientifically worthwhile;
    3. the goals of the research project cannot be achieved in any other way;
    4. the researchers and clinicians have the necessary facilities and skills;
    5. the information materials are readily comprehensible and contain all the details required to permit informed consent (including information on the risks of false-positive or false-negative results, on regulations concerning autopsies and biopsies, etc.);

6. legal and ethical standards are complied with; and
7. parents have the right to be informed of, but also not to be informed of, the results of investigations.

The following **fundamental ethical problems** are raised by research on embryos and fetuses in vivo:

1) Like any other form of human life, embryos and fetuses have an intrinsic dignity. Their claim to protection increases as their development progresses.
2) Embryos and fetuses that are to be the subject of in vivo research live in an inseparable, symbiotic relationship with the pregnant woman. Thus, in all cases, the mother is also affected by such research. However, unlike surplus embryos that are to be used for stem cell procurement, in vivo embryos and fetuses have the potential to be born. If research projects involve lasting or late effects, the special protection criteria that need to be applied are not only those that relate to the situation of pregnancy but also those applicable for neonates and infants.
3) The prime criterion for research on the unborn is that no harm should be caused either to the fetus – irrespective of its developmental stage – or to the mother. If risks are unavoidable, they must always be reduced as far as possible. Risks are not acceptable in the case of research for the benefit of third parties, i.e. research that cannot be justified in terms of therapeutic benefits to the fetus investigated or concerned, or to the unborn child. In cases where it is hoped that research will yield therapeutic benefits for the fetus, unavoidable risks must be justifiable in terms of the therapeutic benefits and must be weighed up against the pros and cons of alternative treatment options (and postnatal treatments in particular). If risks are unavoidable, they must be fully disclosed in advance to the expectant parents. Some contemporary research involving embryos and fetuses is carried out in connection with experimental treatments – treatments for serious defects in the unborn child diagnosed during pregnancy. Research may also take the form of non-invasive investigations, e.g. using ultrasound. It can therefore be assumed that the research in question will be primarily concerned with fetuses at a relatively advanced stage of development. Since we assume that the claim to protection of life becomes stronger in the course of embryonic development, and that the unborn child requires ever-greater protection with the ongoing differentiation of organs and tissues, difficult problems arise in this connection. One example would be a surgical procedure involving an experimental method, carried out on a child that would otherwise be born severely disabled. In extreme cases, such research may represent an alternative to a termination of pregnancy. The extremely difficult question arises of what level of risk may be countenanced if such research is to be justified from the viewpoint of medical ethics. It is clear, however, that if the existing disease or future child's disability constitutes an indication for a termination, not every risk associated with an intervention can be justified, just so long as it is compatible with the child's survival. The aim cannot be to preserve the pregnancy at any price.
4) In the case of a research project which it is hoped will produce therapeutic effects for the fetus/child, the question of whether to perform an experimental procedure may already be raised before the parents have decided whether the disabled child should be carried to term or whether a termination should be performed. The woman cannot be expected in every case to wish to carry the child to term in spite of any disabilities. At any time during the legally specified period, i.e. even after an intervention, the parents/woman should have the right to decide on a termination. The situation is different if the fetus has reached a gestational age at which extrauterine survival is already pos-

sible. In such cases, it must be possible for the decision to be made contingent on the success (or failure) of the intervention. The medical indication for a termination may possibly become applicable.

5) As a general principle, any research carried out on embryos or fetuses in vivo that involves even minimal risk to the embryo/fetus must be directly beneficial to the unborn child itself. From an ethical viewpoint, research for the benefit of third parties is to be categorically rejected. In contrast, non-invasive research not involving any risks may possibly also be for the benefit of third parties, as long as children benefit from the knowledge thus acquired.

6) Many of the ethical questions raised by in vivo research also arise with research projects involving children who are already born. All children – be they born, unborn or at the fetal stage – belong to an extremely vulnerable group in a situation of complete dependency.

7) In the case of in vivo research, voluntary informed consent must always be given both for procedures involving the mother and for procedures performed on the unborn child. Appropriate counselling is to be provided by an impartial external specialist. While the mother can grant informed consent herself, consent must be granted on behalf of the child by the mother or parents. Therefore, as is generally the case for research involving patients or subjects incapable of granting consent, restraint needs to be exercised. The mother is, or the parents are, entitled to withdraw her/their consent at any time without giving any reasons.

8) Legal clarification is required on the question of whether research involving fetuses also includes research involving the placenta, the umbilical cord and the fetal membranes, which also derive from the fertilized oocyte. Since these organs are essential to the survival of the embryo/fetus, the Commission takes the view that research involving these organs should be dealt with in the same way as research on the body of the embryo/fetus.

9) In the case of research studies involving a risk for the mother, for the unborn child or for both, particular attention needs to be paid to the integrity of the (lifelong) mother-child relationship. When a decision is taken to carry out a research project, consideration needs to be given to all the possible consequences (e.g. feelings of guilt on the part of the mother if the experiment is unsuccessful).

10) Another question that arises is whether an embryo is more deserving of protection in vivo than in vitro. The moral status is identical (since «status» is defined in terms of intrinsic dignity and is thus independent of context). Also crucial to the ethical assessment, however, is the question of whether it is possible for a given embryo to develop into a child (i.e. to become an in vivo embryo). If this possibility exists, any research that is carried out has consequences for an unborn child. This leads to greater vulnerability on the part of the in vivo embryo/fetus.

11) Finally, it may be asked whether certain characteristics acquired by the fetus in the course of its development can be considered to represent a moral cut-off point – in particular, viability outside the womb and the capacity to experience pain. The problem can be illustrated by two examples:

- A procedure with a risk of triggering spontaneous expulsion. If a miscarriage occurred, for example, in the 20th week, the fetus would die. If expulsion occurred later, e.g. in the 24th week, the fetus could possibly survive. Does this entail a qualitative difference for research? In describing the risks, the age of the fetus is irrelevant since the consequences are also significant for a fetus over 24 weeks of age, affecting its subsequent life and health. However, in deciding whether and when a procedure is to be performed, the age-dependent chances of survival are clearly an important factor.

- Experimental treatment. If such treatment is performed in a 22-week-old fetus, although there may be a good chance of a successful outcome there is also a high risk of miscarriage or a risk of premature birth (at this age, most neonates will die; those that survive frequently have permanent, severe disabilities due to prematurity). If the treatment is performed in a 30-week-old fetus, the chances of success could be poorer, since maturation in general and organogenesis is further advanced, and less susceptible to corrections. On the other hand, at this age the risk of miscarriage is lower (or the fetus may survive premature birth without disabilities). The possible success of an experimental therapeutic intervention thus needs to be weighed up against the risks to the fetus associated in particular with the timing of the procedure. As decisions of this kind can only ever be based on probabilities, they are highly problematic and require ethical assessment in individual cases.

12) As well as creating new opportunities for health, developments in perinatal medicine and treatment of the fetus during pregnancy also give rise to complex, and sometimes novel, ethical dilemmas. Treatment strategies in neonatal medicine are initiated prior to birth and thus the fetus becomes a patient. The issue of the demarcation and overlapping of peri- and neonatology merits exploration in a separate Opinion.

With regard to the moral status of the embryo/fetus in vivo, it should be borne in mind that moral status does not only arise with increasing developmental age. In the view of the majority of the Commission, the developing human being is endowed with intrinsic dignity from the time of fertilization, which is to be respected and protected. However, the claim to protection of life arises gradually, becoming stronger in the course of embryonic development. With the differentiation of organs, particularly the nervous system, the organism becomes increasingly vulnerable and hence increasingly deserving of protection. In other respects, the Commission takes a critical view of the conventional criteria for determining a moral cut-off point – viability outside the womb and attainment of the capacity to experience pain:

a) In the view of the Commission, **viability outside the womb** does not represent a moral cut-off point. Modern neonatology makes it possible for extremely premature infants to be kept alive (from the 22nd week of pregnancy). The Commission takes the view that the moral status of the fetus does not change when it reaches the developmental age from which it also has a chance of surviving outside the womb. On the other hand, it should be noted that once it leaves the womb, access to the child may be obtained directly rather than only indirectly, via the mother. The fetus thus becomes more vulnerable.
b) In the view of the Commission, attainment of the **capacity to experience** pain likewise does not mark a moral cut-off point. The moral relevance of the attainment of this capacity is questionable, since it must be assumed that the attainment of sensations of pain is associated with the development of sentience and is a gradual process. Convincing reasons would be required to justify the time point mentioned in the set of questions submitted by the SFOPH (20 weeks): how can one know that the capacity for pain only develops in the 20th week of development? The absence of a measurable reaction does not necessarily indicate the absence of sensations of pain. If the capacity for pain were attained suddenly at a detectable point in time, this would represent a possible moral cut-off point for interventions. However, since we assume, as explained above, that no such point can be detected, it is not ethically permissible to adopt the attainment of the capacity for pain as a criterion to legitimize interventions carried out before a given point in time.

Non-invasive embryo research (e.g. in diagnostic procedures) refers to research projects of an observational nature (e.g. the use of microscopic imaging techniques). From an ethical view-

point, procedures involving embryos that are to be used to establish a pregnancy differ significantly from procedures that involve surplus embryos, which would be allowed to die. The NEK-CNE recommends – with a large majority and no dissenting votes – that investigations which are not designed to benefit the embryo concerned («research for the benefit of third parties») should only be carried out on surplus embryos and not on embryos to be used for reproductive purposes. This position is adopted primarily on the grounds that ultimately it is not possible, even with the best available knowledge, to exclude all risks and adverse effects – even in the case of non-invasive methods of in vitro embryo research. At the same time, many matters amenable to non-invasive research can also be studied in embryos no longer intended for reproductive use. Research practices for the benefit of the subject itself – e.g. observation designed to improve treatment and benefit embryos that are to be used for reproductive purposes – cannot be ruled out.

Efforts to treat embryos in vitro are still a long way off. At present, it is difficult to predict or assess the ethical dilemmas that would arise as a result. Logically, only embryos intended to be used to establish a pregnancy would be eligible for treatment efforts or studies with therapeutic intent for the embryo concerned. Such experiments would need to be assessed extremely stringently for risks and side effects, and presumably rejected if there were any doubts. These would be cases (comparable to the creation of chimeras for therapeutic purposes, as mentioned above) not of therapeutically motivated interventions for existing patients, but of the creation of a patient, with a therapeutic experiment planned at the same time. This act of creation could also be omitted without an existing patient suffering, as the latter of course does not yet exist at the time the treatment is planned. For this reason, at this stage, there is no moral duty to provide care for the patient – the so-called «therapeutic imperative» that otherwise ethically motivates medical treatment and care and could justify the acceptance of certain risks is not applicable.