Report of the Bioethics Advisory Committee of The Israel Academy of Sciences and Humanities On:

The Use of Embryonic Stem Cells for Therapeutic Research

August 2001

The Bioethics Advisory Committee of The Israel Academy of Sciences and Humanities*

Section 1.
Why is this an Issue?

1. There is at present a considerable body of researchers who wish to engage in research on a type of human cell known as the stem cell. This research, they argue, will be immeasurably beneficial since it could lead to the development of transplantable tissues for use in the treatment of a wide range of human illnesses that are currently considered difficult or impossible to treat. However, the stem cells in which the researchers are particularly interested are derived from the human embryo, and this gives rise to the question: Is it ethically acceptable to extract cells from a human embryo prior to its implantation *in utero* (thereby ending its potential development) in order to cultivate and study these cells in the laboratory?

Section 2.
The Scientific Background

2. Stem cells are cells that have the ability to develop into more than one form of human tissue. They may be **totipotent –** such as the very early embryo blastomers that are able to develop into all the different types of cells needed for a complete and functioning organism, or **pluripotent** – such as embryonic stem (ES) cell lines

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derived from blastocyst inner cell mass, that are able to produce most types of tissue but are not capable of bringing a functioning organism into existence because they lack the placenta-forming trophoblasts. Embryonic germ line (EG) cells, derived from fetuses at 5–9 weeks, appear also pluripotent. Finally, there are **multipotent** stem cells, able to generate a limited number of tissue types, which are still present in the adult human body. Examples of adult stem cells are certain bone marrow cells that give rise to all blood lineages but can also develop into liver cells, cardiac muscle cells or others. Neural stem cells found in defined brain areas develop into neurons and glial cells but can also develop into heart, lung or liver cells. At the present time, adult stem cells do not appear to have the same potential for proliferation and differentiation as ES cells for preparation of tissues for transplantation. While the safety and ethical issues relating to the uses of adult stem cells, especially from cadaveric sources, are also discussed, the main focus of this report is the ethical aspects of ES cell research.

3. ES cells may be derived from an early embryo at the pre-implantation stage of its development (i.e., at the blastocyst stage, 5–7 days after egg fertilization). The cells of the blastocyst inner cell mass may be cultivated in an artificial medium and allowed to proliferate. The procedure used to extract these cells will prevent that particular embryo from further development. The removal of the cells thus ends the existence of the embryo. The embryo-derived cells are not in themselves an embryo, i.e., they cannot develop into a human being; they are therefore similar to other human tissues, even though they have pluripotent differentiation capability.

4. The ES cells can be kept alive in an artificial medium and will proliferate more or less indefinitely. It is hoped that in the future it will be possible to force these cells to develop into specific tissue types, thus affording the possibility of growing “spare cells or tissues” that can be injected or transplanted into recipients. It is possible that at some future stage this tissue will be used to construct part of or even entire organs for grafting into human hosts whose organs are destroyed or diseased. Such products will have been derived first from embryos, hence the ethical question: is it acceptable to use the human embryo for creating therapeutic products?

Section 3.
Possible Applications of Embryonic Stem Cell Research

5. Many scientists hold the view that the potential benefits to humanity are so enormous that this research should be allowed to proceed. In their view, the benefits considerably outweigh any ethical doubts that surround the procedure.

6. Embryo stem cell research could lead to substantial progress in the treatment of the following conditions (the selection is for purposes of example only):

Nervous System Diseases

7. Many of the conditions that afflict the human nervous system cannot currently be treated or, if treatment is available, can only be treated with difficulty, and the results are disappointing. The use of ES cells may significantly change our ability to repair traumatic lesions such as in the spinal cord, and to combat diseases such as Parkinson's, Alzheimer's, multiple sclerosis or others neuro-degenerative diseases. Laboratory-grown tissues derived from ES cell lines could be used to replace the nervous tissue cells that are lost or damaged in such diseases. It would be possible to transplant neurons that insert themselves in the brain or spinal cord, or produce various neurotransmitters that are lacking. It would also be possible to transplant glial cells that produce the myelin coating around the nerves, which is destroyed in multiple sclerosis. Preliminary work of this nature in animal models has yielded some encouraging results. In the clinic, treatment of Parkinson's patients by transplantation of fetal brain cells (not stem cells) has been practiced on a limited scale and with less than satisfactory results because the fetal cells could not be controlled. The embryo stem cell culture technology could allow to produce safe neuron transplants and allow many more patients to benefit from such novel therapeutic means.

Heart Infarction

8. The heart muscle cells that are destroyed when infarction prevents blood from flowing through coronary arteries could be replaced by "patches" of cardiac muscle cells produced by *in vitro* differentiation of embryo stem cell lines. This has been done

already in mice. Moreover, differentiation of human ES cells into cardiac muscle cells has recently been achieved in Israel.

Bone and Cartilage Diseases

9. Conditions such as osteoarthritis, which involve damage to cartilage, might be corrected by the insertion of cells that repair the damaged joint. Missing bone, resulting from trauma or surgery, might be replaced by newly generated bone cells.

Cancer and Immune diseases

10. Blood and immune cell transplantations, part of cancer treatment, allow more intensive use of cytotoxic anti-cancer drugs. Bone marrow or cord blood employed today for such transplantations could be more efficiently replaced by injections of hematopoietic stem cells derived from ES cells, which have defined immunological potentials or are autologous to the patients. Repair of the immune system using this method would also be highly beneficial in the treatment of immunodeficiencies such as AIDS, or of autoimmune diseases such as lupus, multiple sclerosis or others.

Diabetes

11. The implantation of insulin-producing cells from pancreatic islets has already met with limited success. Xenotransplantation is a promising prospect, but there are major issues of public safety that restrict this option. The cultivation of beta cells derived from ES cells could provide a useful solution to current problems of rejection and shortage of transplantable tissue. This approach has given preliminary positive results in diabetic mice.

Autologous transplants through nuclear transfer technology

12. The risk of transplant rejection or of graft-versus-host disease could be avoided by preparing the stem cells from embryos created by transferring a nucleus from the patient's own cells – a process called nuclear transfer or therapeutic cloning. This procedure involves a reprogramming of the donor cell nucleus in the recipient egg, yielding again pluripotent embryo stem cells. The tissues derived from such stem cells would then be autologous to the recipient and not subject to immune rejection.

Risk assessments and ethics of cell transplantation

13. The benefits from these technologies may also entail some risks that will have to be weighed carefully. One risk may be uncontrolled proliferation of the transplanted cells, or uncontrolled action of these cells in the body of the patient. Genetic control mechanisms for retaining control of the transplanted cells (e.g., cell suicide genes) may be useful. Another risk may be the transmission of infectious agents: this risk would be greater if adult stem cells were used, especially if taken post-mortem. Stem cells from embryos created by nuclear transfer should be carefully examined for risks that may be associated with any possible abnormality in developmental gene expression.

In general, there may be ethical concerns beyond the question of embryo use to produce stem cells, namely the long-term safety of the transplantation procedure. Ethical safeguards must also be established to insure strictly medical uses of stem cell transplantation technologies.

Section 4.
Ethical Debate: The Status of the Embryo

14. The moral legitimacy of performing research on the human embryo depends, in large measure, on the status that one attributes to the embryo. Although there are other considerations that bear on the moral question – such as the modalities of parental consent in embryo donation – the issue of how we define and categorize the embryo at its different developmental stages is crucial to the question of what we can do with it. If the embryo is a human being (or person) then our treatment of it is limited to what we are allowed to do to other human beings. If, by contrast, it is no more than a collection of human cells, then there are far fewer restraints on our handling of it. In the area of stem cell research, much of the moral debate in various countries has focused on the question of just what the embryo is, in particular at the pre-implantation stage.

15. It is clear that the embryo, even at its earlier stages of development, has a unique status in biological terms. Unlike any other cluster of living cells, this cluster has the capacity to develop into a functioning complex organism. This difference may be described as the embryo's potential – the potential to become a fully developed human being. That is, of course, only a biological

fact, but it is a biological fact that has moral implications. Insofar as our moral notions depend upon the valuing of human life, then the human embryo demands respect as being causally and continuously related to human beings who deserve the utmost respect and have human rights. But how far should this respect go when considering the human embryo? Many things in nature are respected but are still permitted to be used by humankind for its benefit. Therefore, the real issue is whether embryos can be accorded full membership of the moral community to which we exclusively admit human persons and human persons alone. At what point does this full membership begin when we consider embryonic and fetal human development?

16. Arguments about whether or not the embryo can be considered a person have been debated in different cultural, philosophical and religious communities and are marked by a failure to reach common agreement. In one view, personhood begins with the fertilization of the ovum by the sperm.[1] From that moment on, the admittedly primitive organism has an identity that will link it continuously to the infant, to the child, and later to the adult human being it will become. To end the life of the embryo, then, amounts to an ending of the future life of the infant and, indeed, of the child and the adult.

17. In the view of others, embryos are entitled to respect but would not enjoy the full personhood enjoyed by persons. It is considered that the human status is acquired at progressive stages during pregnancy and is fully achieved at birth.[2] From a biological standpoint, individuality is not realized at fertilization because one embryo can become two twins. Hence, individual status could be attributed to the embryo only after the day in its early development when division into normal twins is no longer possible (up to 13 days after fertilization). According to some views, ordinary personhood rests on certain conditions that correlate with properties of the human brain, in particular cognitive and emotional infrastructures. Hence, personhood would start when significant parts of that infrastructure form in the fetal brain during pregnancy (for some this may be the third trimester of pregnancy). Accordingly, a younger embryo should be treated with appropriate respect but not as a

1. This is mainly the view of Catholics and many other Christians, see section 5.
2. This is in particular the Jewish view, see section 5.

person. The older it is, the stronger should be the compelling reasons for ending its life (such as a severe threat to the mother's health).

18. A major area of debate is the "potentiality" of the embryo. Some argue that the embryo has the potential to become a person even if it is not yet a person. For this reason, the defenders of the protected embryo status argue that it is wrong to do anything to the embryo that will prevent it from fulfilling this potential. On the other hand, one may argue that the potential to become a human being does not endow the developing embryo with the status of a human being. Ova and sperm are components of the zygote that later becomes a fetus, but we do not accord fetal status to sperm; why, then, accord human being status to an embryo? Moreover, the potential of an embryo to develop into a fetus and a newborn child depends on natural processes that are not one hundred percent successful (for example, in nature, probably only about half of the fertilized embryos result in pregnancy). Therefore, not every embryo has the potential to become a human being.

19. In the case of in-vitro fertilization (IVF), the concept of embryo potential is further complicated since direct medical intervention is needed for the embryo's implantation *in utero*. The rate of implantation is still low, and only about one-third of IVF embryos develop into implantation-competent blastocysts with the normal chromosome structure. There is also a limit to the number of embryos implanted at one time in order to avoid multiple pregnancies. As a result, a fraction of IVF embryos that will not be implanted in a uterus – for medical reasons or because the parents decide against implantation of that additional embryo – has no potential to develop into a human being. The same lack of potential applies to embryos obtained by nuclear transfer, which cannot be implanted under the present interdiction of human reproductive cloning.

20. These scientific and philosophical considerations indicate how intricate is the definition of the pre-implantation embryo status, around which revolves the debate on the ethics of human ES cell research. This bioethical debate occurs in a context of cultural and religious reflection on the nature of human life, from its commencement to its conclusion, and the respect due to human life as such. The opinions expressed by some of the major religions have greatly contributed to the debate, and are compared in the next section.

Section 5.
Religious Views on the Use of ES Cells for Therapeutic Research

I. The Jewish Perspective

21. Jewish Biblical and Talmudic Law holds that human status is acquired progressively during embryonic development only and not at fertilization. In some aspects, the fetus can be considered as a part of the mother's body. Of course, this part should not be removed at will. However, if it endangers the woman's life or severely affects her health (physical and mental), then abortion has to be considered because the status of the mother prevails. The status of the fetus becomes a full human status, equal to that of the mother, only at birth. With regard to the pre-implantation embryo, according to Jewish Law genetic materials outside the uterus have no legal status since they are not even part of a human being until implanted in the womb. Moreover, even in the uterus, only after the first 40 days does the embryo acquire a status as a "formed" human fetus. The status of the embryo outside the womb is comparable to that of gametes, sperm and oocytes: namely, they should not be wasted in vain but may be manipulated for therapeutic purposes. Hence, it is preferable that the embryos be obtained from fertility treatments by IVF.

22. An IVF embryo has the potential to grow into a human being only if implanted in the uterus, but outside the womb (pre-implantation) it has no such possibility (at least with present technologies). If the parents express their decision against implanting certain IVF embryos, these become supernumerary pre-implantation embryos with no more potential to develop into a human being and may be used for reasonable purposes such as deriving stem cells.

23. The commandment to save lives supersedes many other laws in Judaism. Creating embryos by cloning for therapeutic purposes such as deriving cells for transplantation could thus be justified. Given that the materials for stem cell research can be procured in permissible ways, the technology is "morally neutral," i.e., it gains its moral value on the basis of what we do with it. A clear therapeutic aim is, therefore, still essential despite the legitimacy of using pre-implantation embryos. The therapeutic aim should give us the strength not to erect "fences," i.e., barriers resulting from the fear of increasing abortions or the fear of cloning, especially

since such fences could prevent the cure of fatal diseases. Another issue is that of profit: health care is a communal responsibility and social justice is an important value, but one cannot request free altruism; rather one should balance the right of profit with social justice.

The above principles summarize specific statements on Human Embryo Stem Cell Therapeutic Research, published in the US National Bioethics Advisory Committee (NBAC) Report by orthodox Rabbi Moshe Dovid Tendler (Yeshiva University) and liberal Rabbi Elliot N. Dorf (University of Judaism). Opinions on IVF embryos may be found in writings of the late Chief Rabbi of Israel, Rabbi Shlomo Goren or the late Chief Rabbi of the UK, Rabbi Immanuel Jakobovits. A more specific exposition of relevant Halachic decisions on the issue of embryo research is presented in the following section.

II. ES cells theraputic research: Halachic considerations

24. The Jewish Law – *Halacha* – distinguishes between six stages of human maturation. The six stages of human status are:

I. *Pre-implantation embryo* – begins with the fusion of gametes.
II. *Embryo* – begins at implantation, when no active procedure is required to maintain growth.
III. *Fetus* – begins on the 41st day after conception, when gross organogenesis is completed and human form is established.
IV. *Viable fetus* – begins when the fetus becomes viable.
V. *"Dislodged" fetus* – begins at the start of the second stage of labor.
VI. *Neonate* – begins at birth, when the newborn acquires full human status.

Man's creation "in the image of God" confers infinite value on every innocent human life and renders its destruction a capital offense. While this absolute inviolability only begins at birth – stage VI – from an early stage of its embryonic development the embryo enjoys a very sacred title to life, to be set aside only under exceptional circumstances.

The *in vitro* pre-implantation embryo (stage I) is different. The extremely low probability that it will reach the neonatal stage reduces its halachic status; for example, the Sabbath laws are not set aside in order to save its "life." This means that the pre-implantation embryo does not enjoy the same sacred title to life as

an implanted embryo. Nevertheless, as long as the *in-vitro* pre-implantation embryo obtains its implantation potential, its destruction is not essentially different from the deliberate waste of semen. This interdiction is merely the obverse of the biblical precept "be fruitful and multiply;" that is, it implies a prohibition against frustrating the procreative act.

During its first 40 days following conception (stage II), the embryo is considered as "mere water" in the context of the laws of impurity. Some later authorities use this Talmudic source as support for minimizing the embryo's status during this initial period so that the prohibition against "destruction of potential human life" does not exist during this embryonic stage. However, according to other authorities who do not accept this concept, the Sabbath laws *are* set aside in order to save an implanted embryo, which means that an embryo does have some human status in contrast to the *in vitro* pre-implantation embryo.

Halachic Conclusions

1. Jewish law does not differentiate between destruction of an in vitro pre-implantation embryo and its use for routine scientific research. Unless done for the purpose of saving life, both are forbidden as long as the embryo's potential for implantation exists.
2. An *invitro* embryo that has lost its implantation potential may be kept for research even if the research involves the extraction of cells, which implies ending the embryo's capacity to develop.
3. It is forbidden to use a viable implanted embryo for research purposes.
4. The creation of any embryo for such research purposes is prohibited. Nevertheless, the creation of invitro pre-implantation embryos for research should be allowed if it is probable that this research will help to save human life. This includes creating embryos by the cloning technology.
5. There is a clear distinction between the pre-implantation and implanted embryo. However, Jewish law does not recognize the arbitrary 14 day limit or the distinction between embryo and pre-embryo.

III. Christian Views

25. Roman and Orthodox Catholics believe that there is a continuum from the conception to the human person, and that development continues during all stages of life (through both physical and spiritual development to becoming in God's image or Theosis – deification), giving sanctity to all stages of development. The strongest opposition to the use of embryos for research purposes, even therapeutic, is expressed by the Roman Catholic Church. The Holy See, in a note dated 2 August 2000 on ES cells and the status of the embryo, recalls that in the Catholic view a human **person** comes into existence at the time of fertilization. The embryo is therefore considered as a human individual having the right to its own life. Every individual embryo should therefore be given the opportunity to develop into a mature human being. The early embryo is a human person and ending its life by human agency is unthinkable, even for therapeutic applications. IVF procedures, which routinely result in "surplus" embryos created a priori in larger number than will eventually develop into human persons, are not accepted as legitimate by the Catholic Church, making the very source of embryos for stem cell research illicit.

26. Protestant theology is pluralistic and there is not a single source of authority to which reference might be made on the issue of ES cell therapeutic research. It is part of the Protestant ethos that moral questions are determined by the individual conscience. In Protestant thought, Christians may therefore have very differing views on this issue, these views being compatible with Christian beliefs. Some branches of the Protestant tradition consider that full human status is acquired gradually and therefore might not be present in the early embryo. In recent statements, General Synods of the United Church of Christ, while regarding the human pre-embryo as due great respect consistent with its potential to develop into full human personhood, have not regarded the pre-embryo as the equivalent of a person. Hence, the derivation of human stem cells from early embryos, including the creation of embryos by nuclear transfer, should go forward with public funding and at the same time be open to intense public discussion, a discussion which they regard as an essential process of the faith. Lack of public understanding would be very bad for science. The research should never be left unregulated through private funding but be under

nationwide supervision. The objectives should be justified, indicating the benefit for science and medicine and a concern for social justice. The protocols should show respect for the embryos. Other Protestant views consider the dangers of not respecting the weakest human being, namely the embryo, to be greater than any benefit: in other words – it is preferable to abstain or to find other ways of achieving the goals.

27. The US National Bioethics Advisory Committee (NBAC) report, quoting the above diverse Protestant positions, relates also the views of US Roman Catholics, such as Yale theologian Margaret A. Farley who argues for "a return to the centuries-old Catholic position that a certain amount of development is necessary in order for a conceptus to warrant personal status." Considering that science can contribute to an "ongoing process of discernment that remains faithful to..theological and ethical values," she adds: "Embryological studies now show that fertilization ('conception') is itself a 'process,' not a 'moment,' and such studies provide support for the opinion that in its earliest stages (including the blastocyst stage, when stem cells would be extracted for the purposes of research), the embryo is not sufficiently individualized to bear the moral weight of personhood." Views on the embryo change, and the knowledge that twins can derive from a single zygote are not compatible with bestowing "individuality" until the primitive streak is formed. Hence "a growing number of Catholic moral theologians do not consider the human embryo in its earliest stages (prior to the development of the primitive streak or to implantation) to constitute an individualized human entity with the settled inherent potential to become a human person." According to this view, therapeutic cloning for autologous stem cell-derived transplants, but not for reproduction, can also be considered.

IV. Moslem Views

28. In Islam the use of embryos for therapeutic or research purposes may be acceptable provided that it occurs before the point at which the embryo is ensouled, i.e., from the 40th day after fertilization. According to Islamic tradition – in the Koranic sources and Law (*Shari'a*) – the embryonic journey to personhood is a developmental process, and ensoulment may take place after three periods of 40 days, i.e., at 120 days or turn of the first trimester.

However, the embryo is alive in the womb before it receives a soul. Summarizing the legal-ethical discussions of Muslim jurists for the NBAC report, Abdulaziz Sachedina (University of Virginia) concludes: "Most of modern Muslim opinions speak of a moment beyond the blastocyst stage when a fetus turns into a human being. Not every living organism in a uterus is entitled to the same degree of sanctity and honor as a fetus at the turn of the first trimester." Considering this wide time period, decisions in different countries of the Muslim world may vary. Nonetheless, "the following is acceptable to all schools of thought in Islam: The Koran and the Tradition regard perceivable human life as possible at the later stages of the biological development of the embryo…in earlier stages such as when it lodges in the uterus and begins its journey to personhood, the embryo cannot be considered as possessing moral status…jurists make a distinction between a biological and moral person, placing the latter stage after, at least, the first trimester of pregnancy." In conclusion, "In Islam, research on stem cells, made possible by intervention in the early stages of life, is regarded as an act of faith in the ultimate will of God as the Giver of all life, as long as such an intervention is undertaken with the purpose of improving human health."

Section 6.
Options in the Use of Embryos for Stem Cell Research

29. Several categories of embryo may be identified, with different ethical considerations applying in each case. These categories are:

(A) The embryo that is created by IVF in order to be implanted in the uterus and identified as suitable for this purpose.

(B) The embryo that has been created *in vitro* to be implanted as in (A), but which is *supernumerary*, surplus to requirements (excess embryos having to be created to insure successful pregnancy in infertility treatments, some being unsuitable and others no longer needed after pregnancy has begun).

(C) The embryo that is created by oocyte-sperm fertilization for purposes of research or for the development of stem cell lines.

(D) The embryo that is created through transfer into the denucleated oocyte of the nucleus of a donor cell (so-called therapeutic cloning).

First Option: The Supernumerary Embryos

30. If we take into account the view that what gave the embryo moral status in this context was its individual potential to develop into a person to fulfill the parents' desire for procreation, then IVF embryos of category (A) cannot be used for research purposes as long as the parents do not instruct otherwise.

31. Category (B) supernumerary embryos are IVF embryos that will not be implanted as part of the fertility treatment and therefore will never acquire human status through development *in utero*. It is then ethically permissible to allow parents to make a donation of such supernumerary embryos for therapeutic stem cell research. The modalities of the donation should include free informed consent and should respect the dignity of the donors of the embryo. This respect implies explaining the alternatives: keeping the embryo frozen, and the eventual destruction of the embryo. Adequate information should be provided on the benefits that issue from deriving stem cell lines from "non-implantable" embryos for medical applications, i.e., the use of the embryo for the good of others. It may be added that from a scientific point of view, there is no pain or distress to the embryo, which, before the development of neural structures, is not sentient and has no human consciousness.

Second Option: Production of IVF Embryos for Research?

32. The creation of embryos specifically for research purposes (category C) is to be distinguished from the use of embryos that have been created with a view to their implantation but which for reasons mentioned above have not been implanted and have therefore become supernumerary. In the case of the specially created embryo, the act of creation is intended to fulfill a purpose that is a means to something else. This contrasts with the case of the supernumerary embryo, which was not initially seen as a means to another end, but was created as an end in itself.

33. Is there any justification for allowing the creation of embryos in order to extract from them stem cells, which will be used for therapeutic purposes? If the embryo is considered as a human being or person, then this would offend the principle prohibiting the instrumentalization of human beings. However, if it is not considered a human being, there may be no absolute rule preventing its use for the benefit of others, and the potential

medical gains should be weighed against any damage that such a use would entail to any recognized value.

34. Nevertheless, it is essential that upmost care be exerted, since creating embryos for research by fertilization of an ovum with sperm (i.e., not for reproductive purposes) might be viewed by the public as a misuse of IVF technology. Moreover, creating the embryo as a means may be offensive to the donors of the gametes. Creating embryos outside IVF treatments for infertility may also lead to abuse and commercialization of gamete donations.

Third Option: Embryos created by Cloning Technology

35. Nuclear transfer (cloning technology) provides an alternative way of creating human "embryos" that is clearly distinct from normal IVF. The great attraction of this method of creating ES cells lies in the fact that these cells would be compatible with the cells of the donor of the nucleus. This presents major possibilities for autologous transplantation, where the problem of rejection is largely overcome. However, this technique is yet unproven for producing human embryo stem cells.

36. It appears ethically acceptable to create embryos by nuclear transfer in order to produce ES cells for therapeutic purposes. This because, unlike for IVF embryos, sperm and intact ova are not used and the resulting "cloned embryo" could not *a priori* be meant for human reproduction under the interdiction of reproductive cloning, based on the Universal Declaration on the Human Genome and Human Rights and on the technical uncertainties regarding its safety. Reproductive cloning is, indeed, prohibited by the 1998 Israeli Law on Genetic Intervention in Humans (setting a moratorium for a period of 5 years, which will probably be renewed by the Knesset in 2003). However, this Israeli law concerns only production of a complete human being by cloning and does not prohibit creating cloned embryos that will not become human beings through pregnancy. It must be explained, therefore, that this is not cloning in the sense that cloning has been understood in the public debate on reproductive cloning.

37. Nuclear transfer of this sort may be opposed by those who see it as the first steps towards human reproductive cloning. They argue that even if such embryos will not be allowed to develop beyond a very limited stage, such steps will assist the development of tech-

niques that could be used one day in reproductive cloning. Those who support nuclear transfer point out that the benefits of the procedure can take precedence over the fears deriving from this "slippery slope" argument. Even reproductive cloning may one day be a safe technology for which there might be important individual medical applications (such as treatment of total infertility without need for gamete donation from outside the couple, or allowing procreation without fear of transfer of a severe genetic disease by one of the parents carrying this gene). Therefore, some may see the cloning of the embryo as part of the necessary research for such distant goals in the future. (A review on cloning technologies and the potential of ES cells from cloned embryos is found in Appendix 1.)

Fourth Option: Other Sources of Stem Cells

I. Embryonic germ cells

38. Pluripotent embryonic germ (EG) cells can be derived from the developing gonadal ridge of fetuses that are aborted at 5–9 weeks of pregnancy. It is proposed that regulations be considered for the use of such cadaveric fetal tissues for therapeutic research in accordance with the ethical safeguards that exist for fetal tissue transplantation. It must be ascertained that in no circumstance should this become an incentive for elective abortion.

The relative efficiency and safety of this EG cells technology as compared to ES cells for producing transplantable tissues will have to be evaluated.

II. Adult stem cells (multipotent stem cells)

39. Research on the potential of stem cells from different lineages (neural stem cells, hematopoietic stem cells) that can be obtained safely from living persons or from cadaver sources should be continued. There has been much progress in demonstrating the malleability of adult stem cells, in particular bone marrow stem cells that can generate neural cells, liver cells or heart muscle cells. There are still many questions on the practicality of this approach with respect to stem cell expansion and differentiation potentials, as compared with pluripotent ES cells. The risks inherent to the use of adult and cadaver tissues, in particular transfer of pathogenic agents, should also be carefully examined.

The potentialities and limitations of adult stem cells as an alternative to ES cells are described in more detail in Appendix 2.

At present, it does not seem feasible that the existence of adult stem cells should preempt continued research on ES cells, in view of the latter's higher capacity for multiplication and differentiation.

Section 7.
Existing Legal and Regulatory Provisions in Various Countries
General provisions on embryos

40. At the international level, there are few regulatory provisions concerning research on human embryos. Many texts proclaim the right to life in general, e.g., the Universal Declaration of Human Rights of 1948 (Art. 3), the International Covenant on Civil and Political Rights of 1966 (Art. 1), and the African Charter on Human and Peoples' Rights of 1981 (Art. 4). Others more specifically proclaim the right to life of the conceived child, e.g., the American Convention on Human Rights of 1969, which stipulates that the right to life generally begins at the time of conception (Art. 4).

41. At the European level, the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997) does not resolve the issue of the permissibility of embryo research and leaves each country responsible for legislating on this matter, while stipulating two conditions: the prohibition of producing human embryos for research purposes, and the adoption of rules designed to assure adequate protection of the embryo. An Additional Protocol to the Convention, prohibiting all forms of human cloning, was approved in 1998 and took effect on 3 January 2001 in five member states.

The Charter of Fundamental Rights of the European Union, adopted in Nice, France, in December 2000, expressly prohibits eugenic practices and reproductive cloning, but does not comment explicitly on embryo research. In a resolution on 7 September 2000, the European Parliament stated its opposition to the creation of supernumerary embryos and to therapeutic cloning. More recently, the European Group on Ethics in Science and New Technologies to the European Commission adopted *Opinion No. 15* of 14 November 2000 on stem cell research, in which it advocated the allocation of a community budget to research on supernumerary embryos, while pointing out that responsibility for determining the admissibility of such research rested with each member state. On the other hand, it

considered ethically unacceptable the creation of embryos for research purposes from donated gametes and deemed premature the use of nuclear transfer technology (therapeutic cloning).

42. **At the national level**, research on human embryos is permitted in some countries (with varying degrees of supervision), while it is expressly prohibited in others. The second category includes **Ireland**, where Article 40, §3, of the Constitution implicitly prohibits research on the embryo by stating the right to life of the "unborn child" equal to that of the mother. In **Germany**, the law of 13 December 1990 on Embryo Protection regards the fertilization of an ovum for purposes other than its reimplantation in the donor as an offence; it takes the same position on the fertilization of a larger number of ova than can be implanted. The situation is similar in **Austria**, where Law No. 275 of 1992 prohibits the creation of supernumerary embryos. In **Hungary** (Law No. LXXIX of 1992) and **Poland** (Law of 7 January 1993), the life of the unborn child must be respected and protected from its conception. In **Norway**, the law of 5 August 1994 prohibits research on embryos and bans their use for any purpose other than reimplantation in the donor. In **Tunisia**, the National Medical Ethics Committee has stated its opposition to all experimentation on the embryo, which is regarded as a "potential person" (Opinion No.1 of 12 December 1996), as well as to any form of cloning (Opinion No. 3 of 22 May 1997). In **Switzerland**, the Constitution (1999) prohibits the use of medically assisted reproduction for research purposes as well as the fertilization of more ova than are capable of being immediately implanted (Art. 119, letter c). In **Italy**, the bill on medically assisted reproduction specifically prohibits the creation of supernumerary embryos and the early splitting of the embryo for therapeutic or research purposes. The Italian National Committee on Bioethics has rejected reproductive cloning, but was unable to reach a consensus on matters relating to the use of supernumerary embryos and on therapeutic cloning (Opinion of 27 October 2000).

In **Latin America**, the Civil Code of **Argentina** states that the legal status begins at the moment of conception (Art. 63 and 70): in 1994, this principle was embodied as a constitutional right. In **Brazil**, Law No. 8974/95 on genetic engineering prohibits the production, conservation and manipulation of human embryos with a view to their use as available biological material. **Peru** specifically

prohibits human cloning and the fertilization of human ova for purposes other than reproduction (Law No. 26.842). The right to life from the moment of conception is recognized in Peru by the Code of Childhood and Adolescence (Law 27.337), in **Costa Rica** by Law No. 7739 of 1998, and in **Ecuador** by Article 49, §1, of the Constitution (1998).

Recent provisions on ES cell research

43. In a number of other countries, the use for research purposes of embryos donated by persons following a treatment against sterility and not intended for implantation (supernumerary embryos) is permitted. In general, the conditions imposed are the prohibition of research after the 14th day of existence of the embryo and the consent of the couple that supplies the embryo. That is the case, for example, in **Australia**, **Canada, Sweden** and **Finland** (Law 488/1999). In **Spain** (Law 35/1988), research on supernumerary embryos is permitted, but their creation for this specific purpose is prohibited. In September 2000, the Observatory of Law and Bioethics of Barcelona did, however, express its support for the creation of embryos for research purposes, both by donation and by cloning techniques. In **Australia**, the National Health and Medical Council has formulated guidelines, which although not legally binding (the law varies between states) are influential.

44. Finally, certain countries are envisaging authorization of the creation of embryos for research purposes. In the **United Kingdom**, the 1990 Human Fertilisation and Embryology Act authorizes the use of supernumerary embryos for restricted research purposes – in particular concerning reproductive medicine and for the diagnosis of genetic and chromosomal disorders – and the production of embryos for these purposes. On 22 January 2001, the House of Lords passed a law (already approved in December 2000 by the House of Commons) that permits the cloning of human embryos to derive stem cells, thus allowing the possibility of therapeutic cloning. In **France**, Law No. 94-654 of 1994, which prohibits embryo research, is currently under review. In accordance with the opinions delivered by the National Ethics Consultative Committee and the Conseil d'Etat, the draft bill permits the production of stem cell lines from supernumerary embryos for research purposes and therapeutic cloning. In November 2000, **Japan** adopted a law prohibiting reproductive cloning and prescribing the adoption of

directives, which should permit the use of stem cells derived from supernumerary embryos and therapeutic cloning. In the **Netherlands**, a bill is currently being prepared that prohibits the production of embryos for research purposes, with many exceptions. However, the bill authorizes research into stem cells obtained from supernumerary embryos. In **Belgium**, similar bills are being debated in the Senate.

45. In the **USA**, although federal financing of such activities is prohibited, the authorization of research on the embryo is left to the discretion of each state. To date, nine states prohibit such research. In 1999, the National Bioethics Advisory Commission recommended that federal regulations permit research into ES cells obtained from supernumerary embryos. However, it remains opposed to therapeutic cloning and to the deliberate production of embryos for the purpose of obtaining stem cells. In August 2000, the National Institutes of Health issued guidelines on the circumstances in which federally supported scientists might engage in such research. One of the conditions to be met is that no such scientist may destroy an embryo to extract cells: this will have to be done by privately funded scientists, who will then pass the cells on to their publicly funded colleagues. On 31.7.2001, the US House of Representatives voted to ban all forms of human cloning (Weldon bill), a measure that will be reexamined in the Senate.

Provisions in Israel

46. The currently existing Public Health (Extra-Corporeal Fertilization) Regulations, 1987, prescribe terms and conditions for the authorization of retrieving, fertilizing, freezing and implanting fertilized eggs for reproductive purposes. The proscription of ovum retrieval – save for the purpose of fertilization and subsequent implantation in a woman's womb – implies a ban on embryo research, at least in the sense of forbidding the deliberate formation of embryos solely for purposes of research and therapy. The Regulations address neither the question of the fate of frozen embryos at the end of the freezing period nor the issue of supernumerary embryos (i.e., embryos initially formed in the course and for the sake of infertility treatment and not replaced or donated for implantation for some *bona fide* reason). Likewise, the currently proposed law for the regulation of the donation of eggs

for purposes of in vitro fertilization does not address the possibilities of embryo stem cell research.

In 1999, the Knesset (Israeli Parliament) enacted the Prohibition of Genetic Intervention (Human Cloning and Genetic Modification of Reproductive Cells) Act. The proclaimed purpose of this Act is to prescribe a five-year period during which certain genetic interventions in humans may not be conducted, thereby facilitating an assessment of the moral, legal, social and scientific connotations of such interventions and their impact on human dignity. The banned interventions are: firstly, cloning of a human being (defined as "the creation of a whole human being who is absolutely identical, genetically-chromosomically, to another – a human being or an embryo, whether alive or dead"), and secondly, the creation of a human being through the use of reproductive cells (human sperm or egg) that were subjected to germ-line gene modification. The Act provides for the establishment of a multi-disciplinary advisory board that is mandated to follow medical, scientific and biotechnological developments in the field of human genetic research, to submit to the Minister of Health an annual report on such developments, to advise the Minister on these matters, and to offer recommendations with regard to the said prohibitions. The Act further stipulates that the Minister may authorize, by promulgating regulations, the conduct of specific genetic interventions if the Minister considers that such genetic interventions are not violating human dignity, upon the recommendation of the advisory board and subject to prescribed conditions. In such regulations the Minister may set forth the conditions and procedures for granting an authorization, means of monitoring the actual conduct of the authorized intervention, and reporting requirements. The express granting of an authorization must precede the actual performance of the specific genetic intervention in questions. Violators of the five-year ban prescribed by this Act are liable to up to two years imprisonment. Patently, the ban applies only to the two kinds of genetic intervention addressed (human cloning and genetic modification of reproductive cells), but not to other possible modes of genetic research or therapeutic genetic intervention (concerning, for instance, cells and tissues taken from aborted fetuses). Therapeutic cloning is probably not prohibited by this Act.

The Ministry of Health has established a Helsinki Committee for Genetics to examine case by case, and approve or reject applications for genetic research projects involving human beings, including research on pre-implantation embryos. The present report and the following recommendations are aimed at providing the Guidelines for the work of this committee.

Section 8.
Recommendations on Embryonic Stem Cell Research in Israel

Preamble

1. Cultures of human stem cells have the potentiality to yield tissues that, through transplantation, could repair or replace damaged organ tissues. Such transplantations would be life saving in many human pathologic conditions. In addition, scientific research on human stem cells holds promise for increasing understanding on human diseases and cell disorders, and for providing new therapeutic approaches for their treatment.
2. Pluripotent cells of early stage pre-implantation embryos have the broadest potential for derivation of various transplantable cells and tissues. These human embryo stem cells are typically extracted from the inner cell mass of blastocyst-stage embryos produced *in vitro* and maintained for 1–2 weeks without implantation *in utero*.
3. In the medical process of IVF, widely practiced for the treatment of infertility, a certain number of the human embryos produced *in vitro* will not be implanted *in utero* and initiate fetal development and pregnancy. This may be either because of medical reasons, i.e., being unfit for implantation to succeed, or because they are in excess of the clinical need for the reproductive purposes of the parents (supernumerary embryos).
4. In addition to supernumerary IVF embryos, there are other sources of stem cells that are to be evaluated scientifically and ethically. These other sources include adult stem cells, which although only multipotential may have interesting applications. The existence of these stem cells in adult organisms does not preempt the continuous research on pluripotent ES cells, which

appear to have higher multiplication and differentiation potentials.

Specific Recommendations

ES cells from supernumerary IVF embryos

5. Within the framework of IVF treatments, it will be permissible to donate supernumerary embryos that are no longer destined to implantation, and this specifically for the purpose of therapeutic research.
6. Donation must be attained through a process of free and informed consent, and must be regulated to ensure that all embryo donations are made with respect of human dignity, autonomy and liberty of the donors. The possibility of embryo donations should be mentioned from the beginning of the IVF process. The regulations should protect the rights of parents who find embryo research unacceptable.
7. In addition, the regulation should aim at clearly separating the medical team responsible for the IVF treatment and donation, from the medical and scientific teams involved in embryo research who receive the donation. This to ascertain respect of IVF regulations, particularly concerning the number of embryos produced. This separation is also in accordance with the present regulations and practices for organ transplantations in general.
8. Pre-implantation embryos should not be sold or bought. Imperatives of justice and equality in the access to modern medical technologies must be upheld throughout. Public provisions may be made to facilitate access to supernumerary embryos that are in the category allowing donation.
9. Ethical considerations should be part of the information given to donors in the Informed Consent for donating embryos to therapeutic research. In particular:
   i. Consideration of alternatives: One ethical consideration for the donation of pre-implantation embryos no longer destined to implantation for reproductive purposes is that the alternative is the destruction of these embryos or keeping them frozen. Present regulations allow the discarding of frozen embryos after 5 years, unless the

parents instruct otherwise, in accordance with existing IVF regulations.

ii. Morally consistent behavior: Another ethical consideration is that the removal and culture of cells from donated embryos does not entail any lack of respect for human embryos in general. In the same ethical framework, one can consider pre-implantation diagnostics, which implies selection of embryos and discarding some embryos. Pre-implantation diagnostics for genetic diseases has become a medical practice in Israel and many other countries. Other forms of embryo research are already practiced, such as those aimed at improving IVF reproductive technologies. This involves the in vitro growth of fertilized eggs to the blastocyst stage for about one week in order to select the embryos with the highest implantation potential from those devoid of such potential.

ES cells obtained using cloning technologies

10. Although ethically debatable, the Committee considers it ethically permissible to experiment with new in-vitro technologies to produce ES cells, such as reprogramming somatic cell nuclei by transfer into enucleated oocytes (so-called therapeutic cloning, without reproductive purposes). The renucleated oocyte is then cultured without implantation until the blastocyst stage when stem cells are derived from the inner cell mass.
11. Medically, this research holds the highest potential, since the use of a somatic cell taken from the patient in need of transplantation will provide autologous tissues without the danger of graft rejections.
12. The ethical consideration in the creation of such cloned embryonic forms for therapeutic research is that they do not result from sperm and intact ova, and are not meant to be used in any process of complete fetal development since cloning is presently not admissible for reproductive purposes. In fact, the Israeli Law of 1998 on Genetic Interventions in Humans, while prohibiting the creation of a "complete human being" by reproductive cloning, does not rule out producing cloned embryos that will not be implanted.

13. The sources of human oocytes for nuclear transfer should be carefully considered. Such sources could include oocytes from IVF infertility treatments. Voluntary donations of oocytes could be considered from either human donors or from frozen ovarian tissues, in accordance with existing regulations or legislation.
14. An alternative technology to consider may be the reprogramming of somatic cell nuclei by transfer into enucleated cells from pre-existing human ES cell lines, to circumvent the need for enucleated oocytes.

Sources of stem cells other than pre-implantation embryos

15. Scientific research to explore other sources from which human stem cells could be derived should also be continued. These other sources include human tissues taken from fetuses after abortion (embryonic germ cells) and tissues taken from living adults or from cadaver sources.

Embryonic germ cells

16. Pluripotent embryonic germ (EG) cells can be derived from the developing gonadal ridge of fetuses that are aborted at 5–9 weeks of pregnancy. It is proposed that regulations be considered regarding the use of such cadaveric fetal tissues for therapeutic research in accordance with the ethical safeguards that exist for research on fetal tissues and their transplantation. Particular attention should be paid to insure that in no circumstance should the advancement of science become an incentive for elective abortion.

Adult multipotent stem cells

17. Research on the potential of stem cells from different lineages (neural stem cells, hematopoietic stem cells) that can be obtained safely from living persons or from cadaver sources should be continued. There are still many questions on the practicality of this approach with respect to stem cell expansion and differentiation potentials, as compared to ES cells. The risks inherent in the use of adult and cadaver tissues, in particular transfer of pathogenic agents, should be carefully examined.

Ethical Restraints and Conduct of Human Stem Cell Research

18. Research on embryos must be subject to strict supervision and to certain basic constraints. These include the obtaining of full consent on the part of the donors of the biological material and the requirement that the research and possible applications be justifiable in terms of the benefit that it offers humanity. Confidentiality and privacy of the donors should be respected.
19. Research involving the derivation of stem cells from human embryos should be scrutinized meticulously in order to avoid non-scientific or unethical aims. Research should not lead to in vitro culturing of embryos beyond the very early stages of embryonic development (the present limit is 2 weeks).
20. Once ES cell lines have been derived, research should be allowed to be carried out without further need for specific ethical authorization to culture these cells. The usual rules for the culture of human cells should be respected.
21. The medical applications of stem cell-derived replacement tissues for transplantation must be restricted to well-identified therapeutic aims and not for trivial or cosmetic non-medical reasons, or a fortiori eugenic delusions that do not constitute treatment of a disease. Research proposals for such tissue transplantations in human patients should be subject to the usual ethical scrutiny.
22. Imperatives of social justice and equality in benefiting from medical progress must be upheld, and the altruistic nature of this research must be reasonably recognized in the process of embryo donation as well as in the commercial applications of the new therapeutic means and the knowledge gained.
23. If needed, changes in existing legislative regulations regarding embryo or oocyte donations and other appropriate legislative steps should be prepared with the Ministry of Justice and the Ministry of Health. Existing regulations in Israel should be respected, and when necessary changed. New guidelines and regulations specific for Embryonic Stem Cell research should be issued by the Ministry of Health, in keeping with the present recommendations. Guidelines adopted by other countries, such as the UK, should be studied and evaluated, also with the aim of regulating exchange of biological materials from country to country.

24. A national committee, such as the Helsinki Committee for Genetics established by the Ministry of Health, should be instructed in keeping with the present recommendations to examine and eventually approve specific research proposals using human supernumerary embryos for deriving stem cells or using other sources, including cloned "embryos," aborted fetuses and adult sources.
25. It is recommended that public discussions of the issues involved be encouraged in order to provide information, prevent misinterpretations, and examine ways to alleviate fears of misuse of the scientific and technical endeavor concerning human embryo stem cell research. Understanding the conditions under which embryos could be produced a priori for research and therapeutic purposes would be one such issue to debate.
26. The recommended process is to examine the possibilities of insuring the basic human right to benefit from the advancement of science. It should be recalled that the purpose of bioethics is not to ban upfront scientific advances, particularly in the field of medicine, but to define the limits of the socially desirable and ethically permissible.
27. In all aspects of this embryo-related research, particular importance should be given to respect of human dignity and the moral safeguards set out as international principles in the "Universal Declaration on the Human Genome and Human Rights" by the International Bioethics Committee of UNESCO and adopted by the UNESCO General Conference (1997) and by the United Nations Commission of Human Rights (1999).

Bibliography and Sources

1. Annas GJ, Caplan A, Elias S. (1999) Stem cell politics, ethics and medical progress. *Nat Med*, 5, 1339-41.

2. Baguisi A, Behboodi E, Melican DT, Pollock JS, Destrempes MM, Cammuso C, Williams JL, Nims SD, Porter CA, Midura P, Palacios MJ, Ayres SL, Denniston RS, Hayes ML, Ziomek CA, Meade HM, Godke RA, Gavin WG, Overstrom EW, Echelard Y. (1999) Production of goats by somatic cell nuclear transfer. *Nat Biotechnol*, 17, 456-61

3. Brustle O, Jones KN, Learish RD, Karram K, Choudhary K, Wiestler OD, Duncan ID, McKay RD. (1999) Embryonic stem cell-derived glial precursors: a source of myelinating transplants. *Science*, 285, 754-6.

4. Brustle O, Spiro AC, Karram K, Choudhary K, Okabe S, McKay RD. (1997) In-vitro-generated neural precursors participate in mammalian brain development. *Proc Natl Acad Sci* USA, 94, 14809-14.

5. Campbell KH, McWhir J, Ritchie WA, Wilmut I. (1996) Sheep cloned by nuclear transfer from a cultured cell line. *Nature*, 380, 64-6.

6. Cibelli JB, Stice SL, Golueke PJ, Kane JJ, Jerry J, Blackwell C, Ponce de Leon FA, Robl JM. (1998) Cloned transgenic calves produced from nonquiescent fetal fibroblasts. *Science*, 280, 1256-8.

7. Cibelli JB, Stice SL, Golueke PJ, Kane JJ, Jerry J, Blackwell C, Ponce de Leon FA, Robl JM. (1998) Transgenic bovine chimeric offspring produced from somatic cell-derived stem-like cells. *Nat Biotechnol*, 16, 642-6.

8. Deacon T, Dinsmore J, Costantini LC, Ratliff J, Isacson . (1998) Blastula-stage stem cells can differentiate into dopaminergic and serotonergic neurons after transplantation. *Exp Neurol*, 149, 28-41.

9. Dominko T, Mitalipova M, Haley B, Beyhan Z, Memili E, McKusick B, First NL. (1999) Bovine oocyte cytoplasm supports

development of embryos produced by nuclear transfer of somatic cell nuclei from various mammalian species. *Biol Reprod*, 60, 1496-502.

10. Flax JD, Aurora S, Yang C, Simonin C, Wills AM, Billinghurst LL, Jendoubi M, Sidman RL, Wolfe JH, Kim SU, Snyder EY. (1998) Engraftable human neural stem cells respond to developmental cues, replace neurons, and express foreign genes. *Nat Biotechnol*, 16, 1033-9.

11. Friele MB. (Ed.) (2001) *Embryo Experimentation in Europe. Biomedical, Legal and Philosophical Aspects*. Bad Neuenahr-Ahrweiler: Europäische Akademie.

12. Geber S, Sampaio M. (1999) Blastomere development after embryo biopsy: a new model to predict embryo development and to select for transfer. *Hum Reprod*, 14, 782-6.

13. Grifo J. New York University, work presented at the Annual meeting of the American Society for Reproductive Medicine, October 1998.

14. Hole N, Graham GJ, Menzel U, Ansell JD. (1996) A limited temporal window for the derivation of multilineage repopulating hematopoietic progenitors during embryonal stem cell differentiation in vitro. *Blood*, 88, 1266-76.

15. Hottois G. (1998) Is cloning the absolute evil? *Human Reproduction Update*, 4, 787-90.

16. Kato Y, Tani T, Sotomaru Y, Kurokawa K, Kato J, Doguchi H, Yasue H, Tsunoda Y. (1998) Eight calves cloned from somatic cells of a single adult. *Science*, 282, 2095-8.

17. Kikyo N, Wolffe AP. (2000) Reprogramming nuclei: insights from cloning, nuclear transfer and heterokaryons. *J Cell Sci*, 113, 11-20.

18. Kipling D, Faragher RG. (1999) Telomeres. Ageing hard or hardly ageing? [news]. *Nature*, 398, 191, 193.

19. Klug MG, Soonpaa MH, Koh GY, Field LJ. (1996) Genetically selected cardiomyocytes from differentiating embryonic stem cells form stable intracardiac grafts. *J Clin Invest*, 98, 216-24.

20. Lanza RP, Cibelli JB, West MD. (1999) Human therapeutic cloning. *Nat Med*, 5, 975-7.

21. Lanza RP, Cibelli JB, West MD. (1999) Prospects for the use of nuclear transfer in human transplantation. *Nat Biotechnol*, 17, 1171-4.

22. Lanza RP, Cibelli JB, West MD, Dorff E, Tauer C, Green RM. (2001) The ethical reasons for stem cell research. *Science* 292, 1299.

23. Lewis IM, Peura TT, Trounson AO. (1998) Large-scale applications of cloning technologies for agriculture: an industry perspective. *Reprod Fertil Dev*, 10, 677-81.

24. Li M, Pevny L, Lovell-Badge R, Smith A. (1998) Generation of purified neural precursors from embryonic stem cells by lineage selection. *Curr Biol*, 8, 971-4.

25. McDonald JW, Liu XZ, Qu Y, Liu S, Mickey SK, Turetsky D, Gottlieb DI, Choi DW. (1999) Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. *Nat Med*, 5, 1410-2.

26. Meng L, Ely JJ, Stouffer RL, Wolf DP. (1997) Rhesus monkeys produced by nuclear transfer. *Biol Reprod*, 57, 454-9.

27. Pera MF, Reubinoff B, Trounson A. (2000) Human embryonic stem cells. *J Cell Sci*, 113, 5-10.

28. Prather RS, Barnes FL, Sims MM, Robl JM, Eyestone WH, First NL. (1987) Nuclear transplantation in the bovine embryo: assessment of donor nuclei and recipient oocyte. *Biol Reprod*, 37, 859-66.

29. Reubinoff BE, Pera, MF, Fong CY, Trounson A, Bongso A. (2000) Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro. *Nat Biotechnol* 18, 399-405.

30. Revel M. (2000) Ongoing research on mammalian cloning and embryo stem cell technologies: Bioethics of their potential medical applications. *Israel Medical Association Journal* (IMAJ) 2, July supplement, pp 8-14.

31. Revel M. (1998) An outright, upfront condemnation of cloning research is premature. *The Scientist*, 12, p38 (and see Cahier du Comité Consultatif National d'Ethique, October 1997).

32. Rossant J, Nagy A. (1999) In search of the tabula rasa of human cells [news]. *Nat Biotechnol*, 17, 23-4.

33. Schuldiner M, Yanuka O, Itskovich-Eldor J, Melton DA, Benvenisty N. (2000) Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. *Proc Natl Acad Sci* USA 97, 11307-12.

34. Shamblott MJ, Axelman J, Wang S, Bugg EM, Littlefield JW, Donovan PJ, Blumenthal PD, Huggins GR, Gearhart JD. (1998) Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc Natl Acad Sci* USA, 95, 13726-31.

35. Shamblott MJ, Axelman J, Littlefield JW, Blumenthal PD, Huggins GR, Cui Y, Cheng L, Gearhart JD. (2001) Human embryonic germ cell derivatives express a broad range of developmentally distinct markers and proliferate extensively in-vitro. *Proc Natl Acad Sci* USA 98, 113-8.

36. Shiels PG, Kind AJ, Campbell KH, Waddington D, Wilmut I, Colman A, Schnieke AE. (1999) Analysis of telomere lengths in cloned sheep [letter]. *Nature*, 399, 316-7.

37. Solter D, Gearhart J. (1999) Putting stem cells to work. *Science*, 283, 1468-70.

38. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM. (1998) Embryonic stem cell lines derived from human blastocysts. *Science*, 282, 1145-7.

39. Trounson A, Lacham-Kaplan O, Diamente M, Gougoulidis T. (1998) Reprogramming cattle somatic cells by isolated nuclear injection. *Reprod Fertil Dev*, 10,645-50.

40. Tsunoda Y, Yasui T, Shioda Y, Nakamura K, Uchida T, Sugie T. (1987) Full-term development of mouse blastomere nuclei transplanted into enucleated two-cell embryos. *J Exp Zool*, 242, 147-51.

41. Vogel G. (1999) Harnessing the power of stem cells [news]. *Science*, 283, 1432-4.

42. Wakayama T, Yanagimachi R. (1999) Cloning of male mice from adult tail-tip cells [news]. *Nat Genet*, 22, 127-8.

43. Wakayama T, Yanagimachi R. (1999) Cloning the laboratory mouse. *Semin Cell Dev Biol*, 10, 253-8.

44. Wakayama T, Perry AC, Zuccotti M, Johnson KR, Yanagimachi R. (1998) Full-term development of mice from enucleated oocytes injected with cumulus cell nuclei. *Nature*, 394, 369-74.

45. Wakayama T, Rodriguez I, Perry AC, Yanagimachi R, Mombaerts P. (1999) Mice cloned from embryonic stem cells. *Proc Natl Acad Sci* USA, 96, 14984-9.

46. Ward KA, Brown BW. (1998) The production of transgenic domestic livestock: successes, failures and the need for nuclear transfer. *Reprod Fertil Dev*, 10, 659-65.

47. Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. (1997) Viable offspring derived from fetal and adult mammalian cells. *Nature*, 385, 810-3.

48. Wolf DP, Meng L, Ouhibi N, Zelinski-Wooten M. (1999) Nuclear transfer in the rhesus monkey: practical and basic implications. *Biol Reprod*, 60, 199-204.

49. Zawada WM, Cibelli JB, Choi PK, Clarkson ED, Golueke PJ, Witta SE, Bell KP, Kane J, Ponce de Leon FA, Jerry DJ, Robl JM, Freed CR, Stice SL. (1998) Somatic cell cloned transgenic bovine neurons for transplantation in parkinsonian rats. *Nat Med*, 4, 569-74.

Source: ***ASSIA – Jewish Medical Ethics,***
Vol. IV, No. 2, September 2004, pp. 39-54