VIEWPOINT

Europe Confronts the Embryonic Stem Cell Research Challenge

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Europe's historic plurality and the lack of a commonly accepted definition of the moral status of the embryo have led to varying regulation in European countries. Council of Europe and European Union legislation, based on fundamental ethical principles, does exist for specific issues, such as prohibition against producing embryos solely for research. Such principles have recently been elucidated by the European Group on Ethics in Science and New Technologies. Newly emerging research techniques are beginning to cause reconsideration of the regulation of embryo research in Europe.

Is the culturing of human embryonic stem cells really creating a medical revolution? Will it lead toward an entirely new way of practicing medicine in which diseased human body parts can be regenerated with grafts derived from differentiated cells? Will this new medicine of "regeneration" empower society to eliminate the vicissitudes of the natural genetic "lottery," with everyone able to use his or her own cultured cells as a source of new tissues and organs?

No one knows, of course. Nevertheless, the work on embryonic stem cells, reported in *Science* at the end of 1998 (*1*), has given rise to unprecedented hopes, the direct result of which has been new reflection on the status of the human embryo. Such reflection involves reconciling "respect for human life" with "freedom of inquiry," principles that both have constitutional grounds in Europe (*2*).

Throughout human history, the status of the human embryo has continually changed in response to the transformation of cultural values and the acquisition of new scientific knowledge. For the ancient Greek philosophers, for instance, human life per se did not have any value. According to Aristotle, the fetus was deemed worthy of protection only after 40 days for males and 90 days for females. The Catholic Church did not immediately condemn abortion. In the 5th century A.D., Saint Augustine believed that the fetus was part of a woman's body and was thus deprived of any sensation of its own (*3*). It was only in the 13th century that abortion was condemned by the Church as against nature and against a woman's duty to bear children. All the major monotheistic religions, such as Judaism, Catholicism, Protestantism, and Islam, remain divided on the status of the human embryo (*4*).

In today's more secular Europe, opposition continues between those who believe that the human embryo should be respected as a person and those for whom it is essentially a fertilized ovum. However, the principle of respect for human life is strongly rooted in European traditions, and humankind's claim to absolute mastery of the universe is thus often doubted. This is striking in Germany, where religion and a profound commitment to respect for natural processes, combined with the need to reject the Hitler regime's degradation of human life, contribute to a strict prohibition of embryo research (*5*).

Europe's pluralism must be taken into account in understanding the status of embryo research and in predicting its future evolution. Until now, different European countries have taken contrasting approaches, not only on embryo research but also on other subjects such as abortion and new reproductive technologies. On the other hand, uniform European legislation exists on specific issues, namely the prohibition against producing embryos solely for research purposes and against any commercial exploitation, and the forbidding of reproductive cloning and of modifications of the human germ line. Some of these points of agreement seem nonetheless vulnerable in view of the complexity introduced by embryonic stem cell research.

The standard among European countries has been to uphold the principle of respect for the human being from the very beginning of life, and even before birth. This does not mean that the right to life is automatically recognized in the case of the unborn child. The Austrian Constitutional Court decided, for instance, that the right to life "cannot be applied to the embryo" (*6*), whereas the German Constitutional Tribunal ruled to the contrary that the human embryo is a human being fully possessing the dignity of a person (*7*). This results in a great diversity of legislation in Europe with regard to abortion. It ranges from Ireland, whose constitution establishes the "right to life of the unborn child" and results in a strict prohibition against abortion, to France and the United Kingdom, where abortion is generally permitted until the 10th or 12th week of pregnancy.

Similar degrees of diversity exist in national legislation in Europe dealing with embryo research. For instance, in France, although abortion rights are liberal and in vitro fertilization (IVF) is commonly done, embryo research is legally forbidden. In addition, although every European country has abortion legislation, only 7 of the 15 European Union (EU) member states have legal provisions concerning embryo research (*8*): The United Kingdom, which is at the forefront of research, has enacted very liberal legislation to promote embryo research, whereas Belgium has left it unregulated.

None of the European countries has yet dared to define the human embryo or the notion of human life. Thus, it would seem that legislators feel unable to fix in definite terms such concepts that cannot be but arbitrary. The border between life and death is in fact defined according to societal convention. This is made evident by the recent postulation of brain death as the legally determinative event. This new legal standard is linked to the harvesting of organs for transplantation. Similarly, the concept of "pre-embryo" [not older than 14 days after the gametes are mixed (*9*)] has been developed to defuse controversy concerning embryo research.

Does this mean that the definition of such fundamental concepts as human life is bound to be based on fragile principles? In Europe, certainly not. Although it is up to each European state to decide upon the legality of embryo research, in those countries that authorize it, it must be conducted consistent with regulations imposed by European authorities—that is, the Council of Europe (an organization bringing together Eastern and Western European countries) (*10*) and the EU. However, some of these regulations now appear controversial in the context of prospective embryonic stem cell production.

The first regulation is the Convention "on Human Rights and Biomedicine" of the Council of Europe, effective 1 December 1999 (*11*). As already mentioned, although it leaves up to each country the decision to allow or forbid embryo research, it nevertheless requires that countries prohibit "the creation of human embryos for research purposes." Up to now, this seemed sensible because embryo research was mainly connected to new reproductive technologies, and researchers were enabled to experiment with supernumerary embryos. Is this prohibition compatible with research on embryonic stem cells derived by means of nuclear trans-

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fer? Apparently not, and this is probably one of the reasons why certain European countries are hesitating to ratify the Convention.

At the EU level, the regulation "on the Legal Protection of Biotechnological Inventions," dated 6 July 1998 (*12*), considers "the use of embryos for industrial and commercial purposes" to be unpatentable inventions. Is this prohibition, referring to the older European principle of "the noncommercialization of the human body," in accordance with the patenting of cultured stem cells? That is another question now being raised.

What is lacking is a clarification of the European values at stake in this field. It is a void that the European Group on Ethics in Science and New Technologies (EGE) has endeavored to fill, with half of its 14 Opinions to date touching on the ethics of embryo research (*8*). The EGE, created in 1992, is an advisory committee to the European Commission, the European Parliament, and the Council of Ministers of the EU. It is independent, represented by 12 countries and several disciplines (philosophy, law, medicine, biology, sociology, theology, and computer science) (*8*).

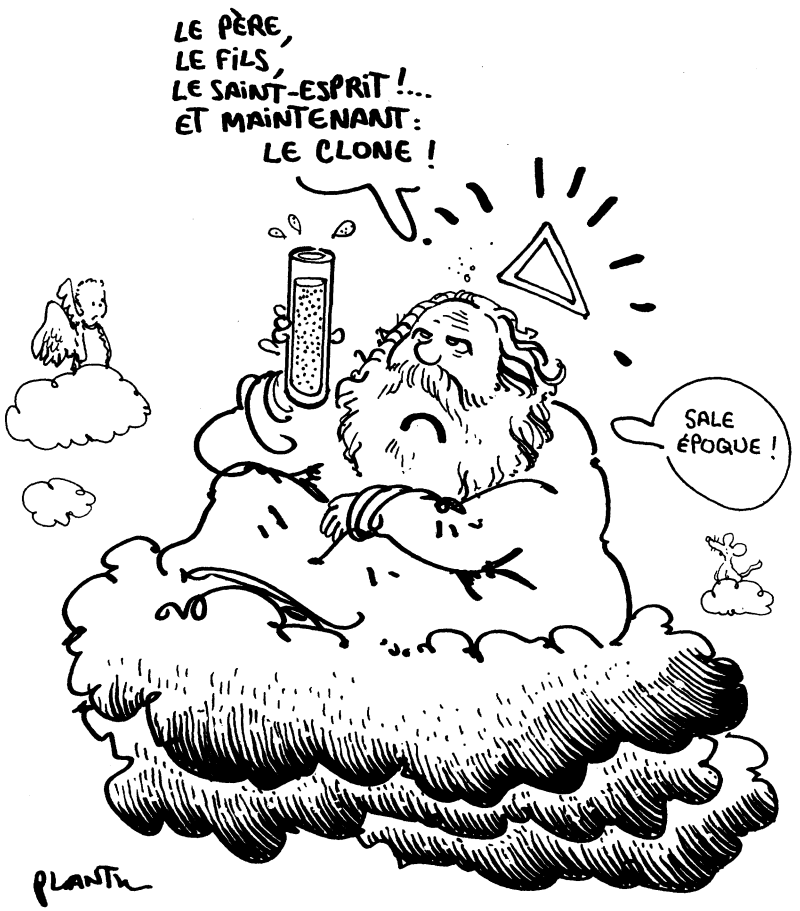
The EGE has taken into account the facts that there is no specific legislation at the EU level concerning embryonic stem cell culturing and that there currently is no real will to harmonize national laws. "Because of lack of consensus concerning the status of human embryos, it would be inappropriate to impose one exclusive moral code," admits the EGE in its opinion on "Human Embryo Research." Accordingly, the EGE has refused to call for a ban on public funding for embryo research at the European Community level, in contrast to the United States, where Congress has prohibited federal funding for embryo research, leaving it in private hands. The EGE stressed that "it is crucial to place human embryo research, in the countries where it is permitted, under strict public control, while ensuring maximum transparency, whether the research in question is carried out either by the public or by the private sector."

In this context, all solutions that might be adopted in Europe concerning embryonic stem cell research will satisfy the following conditions:

First, the principle of human dignity is stronger in Europe than the principle of unrestrained freedom of research. This explains why there is a general ban at the European level on reproductive cloning and on human germ line modifications, both in the aforementioned regulation "on the Legal Protection of Biotechnological Inventions" and in the decision of the EU to refuse funding for such research (*13*). The issue here is that embryo manipulation raises completely different ethical concerns, depending on whether it is intended for research or for procreation. As the EGE said in its opinion on cloning: "Considerations of instrumentalization and eugenics render [reproductive cloning] ethically unacceptable," but this is not the case for human embryo research, notwithstanding the fact that such research otherwise raises "serious ethical controversies" (*8*).

Second, irreversible damage is possible unless strong emphasis is placed on the principle of adequate caution ahead of the pursuit of economic interests. As a consequence, ethical evaluation and open public debate must come before research in the most controversial areas. Debate is all the more essential given the possibility of embryonic stem cells being used on an industrial scale. The EGE stresses: "However promising the medical perspectives, recent manipulations of human stem cell lines carried out in the U.S. raise a number of ethical questions. These questions emphasize the urgency to enlarge the debate. . . . European citizens have a right to be clearly informed . . . as well as to be put in a position to evaluate the responsibilities implied for society as a whole" (*8*).

In conclusion, embryonic stem cell research in Europe will ultimately depend on European citizens' values. As Rabelais said in 1532, in his book *Pantagruel* (*14*), "Science without conscience is but death of the soul." In the light of today's preoccupations in Europe, this statement should be understood as reflecting two cultural currents. First, Europeans hold the view that public authorities must establish the principles according to which research must be conducted. Second, because of Europe's experience of scientific excess, there is a consensus that the scientific agenda should be congruent with fundamental social values.



The cartoon depicts a European perspective on cloning, as illustrated by Plantu in the French newspaper *Le Monde* (13 January 1998). Translation: "The Father, the Son, the Holy Spirit—and now: the Clone! Hard times!" (Reprinted by permission of the illustrator)

References and Notes

1. E. Marshall, *Science* **282**, 1014 (1998); *Science* **282**, 1962 (1998).
2. According to Article 2 of the European Convention for the Protection of Human Rights and Fundamental Freedoms, signed in Rome on 4 November 1950, "Everyone's right to life shall be protected by law . . ."
3. J. T. Noonan Jr., *Contraception, a History of Its Treatment by Catholic Theologians and Canonists* (Harvard Univ. Press, Cambridge, MA, 1965).
4. A. McLaren, *A History of Contraception from Antiquity to the Present Day* (Blackwell, Oxford, 1990).
5. E. Deutsch, *Med. Law* **12**, 535 (1993).
6. Quoted by M. Knoppers in *Human Dignity and Genetic Heritage* (Reform Commission of Canada, study document in the "Protection of Life" series).
7. Decision of the Constitutional German Federal Tribunal about the Abortion Act, 25 February 1975, *Entscheidungen des Bundesverfassungsgerichts*, Tome 39, p. 37.
8. For more details, see *Science* Online (www.sciencemag.org/feature/data/1047249.shl).

9. Article 3 of the UK Human Fertilisation and Embryology Act (Her Majesty's Stationery Office, London, 1990).
10. The Council of Europe is an international organization established in the wake of the Second World War, whose main role is to strengthen democracy, human rights, and the rule of law throughout its member states. For further information, see (*8*).
11. The Convention has been ratified by, and is thus applicable in, six countries: Denmark, Greece, San Marino, Slovakia, Slovenia, and Spain.
12. Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (Official Journal of the European Communities, L 213, vol. 41, 30 July 1998).
13. Decision No.182/1999/EC of the European Parliament and of the Council, of 22 December 1998, concerning the Fifth Framework Program of the European Community for "Research, Technological Development and Demonstration Activities" (1998 to 2002) (Official Journal of the European Communities, L 26/1, 1 February 1999).
14. F. Rabelais, *Gargantua and Pantagruel*, B. Raffel, Transl. (Norton, New York, 1991).

REVIEW

Out of Eden: Stem Cells and Their Niches

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Stem cells are currently in the news for two reasons: the successful cultivation of human embryonic stem cell lines and reports that adult stem cells can differentiate into developmentally unrelated cell types, such as nerve cells into blood cells. Both intrinsic and extrinsic signals regulate stem cell fate and some of these signals have now been identified. Certain aspects of the stem cell microenvironment, or niche, are conserved between tissues, and this can be exploited in the application of stem cells to tissue replacement therapy.

Introduction

Stem cells are very much in the news. The announcement that pluripotent stem cells can be cultured from aborted human fetuses or from spare embryos from in vitro fertilization procedures (*1*) has been greeted with both enthusiasm and opprobrium. The potential medical use for tissue replacement therapy is very exciting, but commentators are understandably cautious given the unresolved ethical questions. Less controversial, but equally newsworthy, is the spate of reports that stem cells derived from adult tissues have much wider differentiation potential than was previously thought (*2*). The hope is that this hitherto unrecognized plasticity can be exploited to generate cells for autologous tissue grafts.

The spotlight on stem cells has revealed gaps in our knowledge that must be filled if we are to take advantage of their full potential for treating devastating degenerative diseases such as Parkinson's disease and muscular dystrophy. We need to know more about the intrinsic controls that keep stem cells as stem cells or direct them along particular differentiation pathways. Such intrinsic regulators are, in turn, sensitive to the influences of the microenvironment, or niche, where stem cells normally reside: What is this Garden of Eden from which stem cell descendants are evicted to face differentiation and death?

What Exactly Is a Stem Cell?

Although this question remains contentious after 30 years of debate (*3*) the prevailing view is that stem cells are cells with the capacity for unlimited or prolonged self-renewal that can produce at least one type of highly differentiated descendant. Usually, between the stem cell and its terminally differentiated progeny there is an intermediate population of committed progenitors with limited proliferative capacity and restricted differentiation potential, sometimes known as transit amplifying cells (Fig. 1). In situations that involve a single differentiation pathway, such as interfollicular epidermis, the primary function of this transit population is to increase the number of differentiated cells produced by each stem cell division. This means that, although a stem cell has high self-renewal capacity, it may actually divide relatively infrequently.

Classically, mammalian stem cells have been studied in tissues such as blood and epidermis, where the differentiated cells do not divide and have a short life-span. However, stem cells are also present in tissues that normally undergo very limited regeneration or turnover, such as the brain and liver. In early embryos, stem cell self-renewal is less important than the ability to found specific lineages and, paradoxically, it is as a result of differentiation that embryonic stem (ES) cells give rise to the stem cells of adult tissues.

Stem cells can sometimes be identified quite precisely by their morphology or location. In the *Drosophila* gonad and peripheral nervous system (PNS), for example, stem and nonstem daughters have a well-defined orientation with respect to the surrounding cells (*4*) (Fig. 2). However, in many other tissues, the position of the stem cells is known only approximately, and panels of molecular markers have been developed to define the stem cell compartment or pool. Such markers may provide important clues about how the stem cell phenotype is controlled. Epidermal stem cells, for example, express high levels of β1 integrins, and β1 integrin–mediated adhesion to extracellular matrix suppresses the onset of terminal differentiation (*5*, *6*) (Fig. 3).

Strategies for Stem Cell Self-Renewal and Differentiation

There are two general strategies by which stem cells generate differentiated progeny (*3*). At one extreme, there are mechanisms that might be described as invariant, in which a stem cell gives rise, through an asymmetric cell division, to one stem daughter and one daughter that undergoes differentiation (Fig. 1A). Examples abound in unicellular organisms and invertebrates (for example, *Drosophila* ovary) (Fig. 2).

At the other extreme (Fig. 1B; Fig. 3) are highly regulative mechanisms in which a stem cell gives rise to daughter cells that have a finite probability of being either stem cells or committed progenitors. Most mammalian self-renewing tissues fall into this category. At steady state, each stem cell division gives rise, on average, to one stem and one committed daughter, but asymmetry is achieved on a population basis rather than at the level of individual cell divisions. Furthermore, in some tissues there may be a continuum of cell behavior, with stem and progenitor cells at opposite ends of a spectrum, instead of discrete stem and progenitor populations (*5*, *6*).

Although the two strategies are mechanistically very different, both involve multiple feedback controls and reciprocal intercellular interactions. Populational asymmetry facilitates the response to variable physiological need, as when increased production of blood or epidermal cells is required after an injury. Nevertheless, potential flexibility in the invariant strategy has been revealed experimentally by ectopically expressing regulatory factors in non–stem cell daughters (*4*).

Intrinsic Controls of Stem Cell Fate

Maintenance of the stem cell compartment ultimately depends on cell autonomous regulators modulated by external signals. Such intrinsic regulators include the proteins re-

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