Differing Routes to Stem Cell Research: Germany and Italy

edited by
Renato G. Mazzolini / Hans-Jörg Rheinberger

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Introduction

The Weight of the Past

by *Renato G. Mazzolini**

When considering our present age of manipulation technologies in light of the researches carried out by biotechnologists, and in light of their results, discoveries and applications both actual and possible, there is only one statement that, as a historian, I feel confident in making: that we are living through a long period of transition in biopolitics driven also by those results and discoveries. It is a period which started with recombinant DNA technology in the early 1970s and whose end nobody is able to foresee. Not even science fiction writers! Many of the views with which people of my generation were brought up have now dramatically changed. A good number of notions, categories and definitions that were taken for granted around forty years ago have become untenable. Thus, familiar distinctions that seemed clear-cut, such as those between nature and culture, or moral and immoral, have been discarded following the discoveries and applications of biotechnologists. For instance, transgenic plants and animals no longer fit with our traditional definitions of what is natural and what is cultural, and sociologists term them 'hybrids'.

Such distinctions used to be essential for the political and social order of society because they furnished a recognizable frame within which legislators could order the world, as well as human actions. But the frame has been broken in many points, showing at the same time that such distinctions have become obsolete and that outside our traditional frame there lies a vast and unknown territory which requires exploration, and possibly incorporation within a new frame still to be constructed.

Breaking frames and investigating what lies outside them has been a distinctive feature of Western science since at least the sixteenth century. This is – in my view – a feature pertaining to the practical ethos of science. Rebuilding the frame so that it can incorporate new territories

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is part of the work undertaken by politicians, religious and legal institutions, intellectuals, scientists as experts and citizens to provide new (and not old) answers to new problems. And it is in this rebuilding of the frame that the weight of the past may well be perceived in the legal solutions developed by each nation-state.

During the past thirteen years – i.e. since human embryonic stem cells were first isolated and cultured – extensive research has been devoted to both adult and embryonic stem cells. Because of their potential use in regenerative medicine and the controversial issues concerning reproduction and embryo experimentation, impressive debates on many implications of stem cell research have taken place in the public sphere (newspapers, magazines, radio and television programmes, the internet), in parliaments, in religious communities, as well as in more specialised arenas such as those of bioethicists and jurists.

The most significant of these debates has concentrated on the status of the early human embryo, and it has been closely related to previous debates on parliamentary bills to regulate abortion, in vitro fertilisation and cloning (animal, human, therapeutic and reproductive). Since 1998, primarily scientists, but also ethicists and legislators, have been faced with a huge dilemma between the reasonable hope of curing disease with embryonic stem cells and the destruction of an early embryo in order to provide stem cells for research. Positions have ranged from the view which considers the early embryo, from the moment of fertilisation, to be a human being, or a person, to the view which considers it an undifferentiated collection of cells deserving no more deference than any other collection of human cells.

This dilemma has generated a conflict between values and the norms and regulations that could be adopted. As in most conflicts – which are typical of transition periods – different strategies and forms of propaganda have been deployed by the interested parties according to their relative strength and alliances. And the conflict has spread to numerous detailed questions, such as, for instance, what should be done with surplus frozen embryos.

However, with the publications of the papers on induced pluripotent stem (iPS) cells by Yamanaka and co-workers in 2006 and 2007, and by Thomson and co-workers in 2007, a technical solution to avoid the destruction of an embryo has been found. In fact, those papers showed

that adult cells may be «reprogrammed» to return to their embryonic-like state, and they demonstrated that the development of stem cells is not necessarily a one-way process. According to many experts, this discovery put an end to the ethical controversy, and therefore to the conflict. According to other experts, however, research on embryonic stem cells should continue because they provide the golden standard to gain better understanding of human development and regeneration processes. Recently, indeed, the US government has unfrozen public funding for embryonic stem cell research.

Advances in stem cell research have generated a succession of seismic effects not only in the biomedical sciences but also in other specialised research fields, such as those of bioethics and jurisprudence, but most of all within the public arena, where it has forced politicians in different European countries to promote legislation either enabling or restricting stem cell research.

It is well known that the United Kingdom has introduced legislation which is more amenable to demands put forward by scientists. Its strategy is inclusive. Other nation-states have adopted more defensive strategies. For instance, Germany – which has had an *Embryo Protection Act* since 13 December 1990 – passed two laws on stem cell research in 2002 and in 2008. The Italian Parliament enacted a law on medically assisted procreation only in 2004, but no law concerning stem cell research. The latter is indirectly regulated by law 40/2004, although it makes no mention of stem cells. These are significant differences. It seems to me that – albeit with great caution – Germany has responded more promptly to the changing realities of science, whilst Italy has tended to delay any response.

While the United Kingdom has a long-standing tradition in assuming the risks of regulated liberties, in other countries, such as Germany and Italy, the weight of the past has produced – in my view – defensive strategies. In the case of Germany, the main cause of such strategy has been the fear of introducing norms that might recall northern eugenics and national socialism. This fear has been equally spread across political parties, religious institutions and social movements. On the other hand, institutions and scientific committees enjoy high credibility in Germany. In the case of Italy, instead, the debate on stem cell research has reproduced a traditional confrontation between Catholics and

laici, with the result that all political parties (with the exception of the Radical Party) have feared conflict with the Catholic Church and the consequent loss of Catholic votes, since Catholics are present in most political parties. Unlike German politicians, Italian ones have chosen to evade the questions posed by the public debate. Furthermore, scientific committees in Italy do not have people's confidence as they do in Germany, because their members are considered to be selected on the basis of their political alliances rather than their expertise.

The papers in this book were presented at a small conference held at the Istituto storico italo-germanico in Trento on the 21st and 22nd of September 2010. It was organized by Professor Rheinberger, and myself, and financed by the Max-Planck-Institut für Wissenschaftsgeschichte, Berlin and the Project «Science, Technology and Society» of Trento University with the aim of providing an overview of the differing routes to stem cell research in Germany and Italy until the present, with special regard to debates in the public sphere. It was not intended to be a conference on bioethics, and therefore our contributors are historians, biologists, jurists and sociologists.

Since the early Middle Ages, the inhabitants of what we now call Germany and Italy have had much more of a common history and a common culture than is usually assumed. 'Common', of course, does not mean either identical or peaceful. In matters of biopolitics, for instance, they partially diverged in the 1930s and early 1940s. Less so in the present. The regulations and restrictions under which stem cell biologists must work are similar, so that both countries have similar problems to solve if they wish to participate in building that very frame in which future biopolitics will take place. But they differ deeply – and this is my point – in what Sheila Jasanoff calls in her admirable book *Designs on Nature*, «civic epistemologies». Over a year ago a young colleague of mine asked me: «But do you really think that Italy has a civic epistemology at all?» I answered «Yes». A long correspondence followed, but the matter remained unsettled. I hope that some of the contributions to this volume may shed some light on this question as well.

A Revolution in Biology?

by *Hans-Jörg Rheinberger**

It is always advisable, in science as elsewhere, not to use the term «revolution» in an inflationary manner, but rather with caution. Hence the question mark in the title, «A Revolution in Biology?», is more than appropriate. Nevertheless, there has been and there is widespread talk about a revolution in the context of research with respect to stem cells, and with it, the developmental phenomena of toti-potency and pluri-potency. Especially over the past few years, the possibility of re-programming differentiated cells and of setting them back, as it were, to a more or less undifferentiated state, has been arousing excitement. But if we adhere to the notion of revolution, we will have to ask more precisely: A revolution of what? And moreover: What does 'biology' mean here?

What I have to say on the topic in these introductory remarks on our workshop is very general, even hyperbolic to some extent, and thus meant as a stimulus for discussion rather than as a considered, not to say exhaustive, assessment of the present state of stem cell research. What follow are instead musings, an interjection of an historical epistemologist, and thus an outsider, or at best an observer of a field that is moving at a breathtaking pace today.

Most biologists will probably agree that, nevertheless, we are obviously still far from an encompassing mechanistic understanding of the details of differentiation, or of development for that matter – more and more frequently called «epigenetics» these days – in higher animals in all their intricacy. A few molecular principles are known, to be sure, and a Nobel Prize was awarded for these findings fifteen years ago (1995, Christiane Nüsslein-Volhard, Edward Lewis, Eric Wieschaus). Have really novel and basic molecular insights been added since then? I doubt that this is the case, at least not to the extent that one can speak of a revolution. Hence, if there is something like a revolution with respect to stem cell

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research, it must lie somewhere else; not, as it were, at the level of the conceptualization and identification of basic developmental mechanisms. The title of my brief statement – «A Revolution in Biology?» – thus needs to be qualified with respect to both of its parts.

Here, in short, is the assessment that I have to offer. It is twofold. First, there is the biological perspective. I would claim that what we are witnessing today is something like a revolution in 'experimental technology', that is, the manipulation of cells *in vitro*. The core of this revolution has to do with what is being called «re-programming.» The first climax of re-programming came with the successful implantation of the nucleus of a differentiated somatic cell into an enucleated egg of a sheep, from which Dolly resulted some fifteen years ago. In this and in subsequent similar experiments, including human eggs, the re-programming is effected by the egg's cytoplasm in bulk. Consequently, not much is to be learned about its molecular details. The outcome of this experimental feat, to speak frankly, appears to be more of the order of the spectacular than the really scientific: The surprise lies in the fact that it works. Not so with the second climax, the one that is now happening under our eyes: the re-programming of specialized somatic cells into what is called «induced pluri-potent stem cells» (iPS cells); that is, cells with the characteristics of stem cells. Since de-differentiation here is induced by the introduction into the cell of specified genes and/or other factors such as proteins, or small molecules, there is the potential to learn a great deal about the molecular details of de-differentiation and vice versa, that is, of differentiation as a consequence. Epistemologically, this is a new variant of the theme of 'learning by default', one of the most important and productive experimental strategies in the life sciences since they turned experimental with experimental physiology in the nineteenth century.

But second, there is also a medical perspective that may amount to a revolution in medical research. I deliberately speak of a revolution in 'medical research' here, and not of a revolution in medicine in terms of diagnostics or even therapeutics. «Regenerative medicine», as it is now being called, may be on the horizon, but this is, if I see it correctly, a still rather remote horizon at the moment. This may be seen as the spectacular aspect, again, although in this case not as a fact, but rather as a promise about life. But I am once again concerned here with an 'epistemological' observation that has, to be sure, an ethical dimension as well. The prospect of mimicking differentiation processes via cell proliferation in a Petri dish or in a cell

growth reactor by using human-derived cells confronts us with a very peculiar situation. It already limits, and may further limit to a dramatic extent, the use of animal models in medical research. The circumvention, or better, the short-cutting of animal models, however, does not at all mean the end of the use of 'models' in medical research altogether. It rather means the use of human models. Medical research always needs surrogates. And modeling always means, to a certain extent, modification. We are confronted with a new form of experimentation on human living material and, to put it succinctly, human modification. This new experimental regime has a precarious status. On the one hand, it is not to be qualified as experimentation on human subjects that would fall under an *a priori* ethical verdict. On the other hand, nor is it to be qualified as *a priori* unobjectionable ethically: it concerns cells that have the potential to give rise to human beings. It has thus a precarious status in and of itself, not because definitions or conventions are lacking. This is the theoretical core of the current debate around stem cells: a new form of the dilemma as to what is judged to be experimentally allowed with the prospect of, and under the premise of, saving future lives.

Historical Perspectives

Where Does Stem Cell Research Stem from?

A Terminological Analysis of the First Ninety Years

by *Ariane Dröscher**

1. *Introduction*

One of the main difficulties that emerge when scientists, politicians, lawyers and the broad public meet regards communication. The terminology used in these debates often means different things for different people. One outstanding example of these mostly latent misunderstandings is the term 'stem cell'. Not even attempting to solve this riddle, the aim of this paper is to give insight into the intrinsic complexities that the term has accumulated during its migration through different disciplinary, conceptual, experimental, and historical contexts. The analysis will mainly concentrate on the period 1868-1960. Even this temporal limitation cannot avoid only partial consideration of the literature.

The history of stem cell research is normally considered a recent one. Several 'birthdays' are indicated, especially 22 February 1997, the day of the public announcement in «Nature» of the first successfully cloned animal (although Dolly the sheep had already been born on 5 July 1996), or 6 November 1998, when James Thomson and his coworkers at the University of Wisconsin-Madison reported in «Science» that they had succeeded for the first time to isolate and cultivate *in vitro* human embryonic stem cell lines[1]. This may also be the reason why there still is no real historical analysis: the story is simply too recent.

Yet stem cell research is becoming more complex and increasingly unable to specify what exactly distinguishes a stem cell from a 'normal' cell.

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[1] I. WILMUT et al., *Viable Offspring Derived from Fetal and Adult Mammalian Cells*, in «Nature», 385, 1997, pp. 810-813; J.A. THOMPSON et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, in «Science», 282, 1998, pp. 1145-1147.

Consequently, the view of researchers has begun to broaden and the historical reviews are now less triumphant and more investigative. The difficulties are understandable bearing in mind that, far from being a simple technology or commodity, the study of stem cells delves into the question of life itself, and thus touches on questions that have been on the agenda of biological inquiry for a long time. There are at least nine disciplines or research fields which have contributed to stem cell research: botany and horticulture; cell theory; evolutionary biology; embryology and developmental biology; hematology; cell and tissue culture; regeneration biology; teratology and teratogeny; and cancer research. Moreover, concepts and tools from systems biology, genetics, molecular biology, radiobiology and still other fields have been integrated. Each of them has contributed to research with slightly different terminologies, definitions, tools, model organisms, institutional infrastructures, social authorities, expectations and fears, and ethical-legal discussions. All of these overlapping dimensions influence how sense is made of natural phenomena[2]. This essay, however, will focus principally on only one of these categories, namely on the terminology, and hence on the questions of when, how, and by whom the term 'stem cell' has been used (or not used) and on the extent to which it was thought that the word coincided with a real ontological entity.

Words are carriers of understanding[3]. And to a certain degree words continue to influence our reasoning even when the original intentions of the name-giving are no longer known or when the original meaning is no longer shared. In the case of stem cells, I shall seek to show how the term still shapes our way of explaining the capacity of living matter to entirely or partially self-renew.

[2] See e.g. A.E. CLARKE - J.H. FUJIMURA (eds), *The Right Tools for the Job. At Work in Twentieth-century Life Sciences*, Princeton NJ 1992; M. LEDERMAN - R.M. BURIAN (eds), *The Right Organism for the Job*, in «Journal of the History of Biology», 26, 1993, 2, pp. 205-381; L. DASTON (ed.), *Biographies of Scientific Objects*, Chicago - London 2000. G. TESTA, *Stem Cells through Stem Belief: The Co-production of Biotechnological Pluralism*, in «Science as Culture», 17, 2008, pp. 435-448, and the other papers of this volume.

[3] Much has been written on the role of metaphors in science; see e.g. T.L. BROWN, *Making Truth: Metaphor in Science*, Urbana IL 2003; F. HALLYUN (ed.), *Metaphor and Analogy in the Sciences*, Dordrecht et al. 2000; S. MAASEN - P. WEINGART, *Metaphors and the Dynamics of Knowledge*, London - New York 2000.

2. *A short etymology of the term stem (cell)*

Recent analyses on scientific terminology emphasize that the impact of names goes beyond the simple denoting of research objects or disciplines. Soraya de Chadarevian, for example, maintains that the name 'molecular biology' was introduced as a strategic tool, whereas Jane Maienschein has shown how the word 'embryo' influences the present-day debate on embryonic research[4]. The way in which a name is conferred and by whom, however, is highly variable[5]. The names of disciplines often refer to the object of inquiry, like embryology or anthropology, or to a somehow congruent group of objects which are investigated, like bacteriology or ultrastructure research. The name 'molecular biology', on the other hand, stresses the technological approach, 'genetics' a vital process (that of genesis), comparative anatomy a scientific activity (that of comparing), 'genomics' and 'systems biology' nothing less than «a new way of thinking about biology»[6]. The origins of the names of scientific objects are even more singular and heterogeneous. Notably, the term 'cell' derived from Robert Hooke's impression of seeing many closed spaces, like monk cells, in cork[7].

4 S. DE CHADAREVIAN, *Designs for Life. Molecular Biology after World War II*, Cambridge 2002, p. 206; J. MAIENSCHEIN, *What's in a Name: Embryos, Clones, and Stem Cells*, in «American Journal of Bioethics», 2, 2002, 1, pp. 12-19; J. MAIENSCHEIN, *Whose View of Life? Embryos, Cloning, and Stem Cells*, Cambridge MA 2003.

5 A. POWELL et al., *Disciplinary Baptism: A Comparison of the Naming Stories of Genetics, Molecular Biology, Genomics, and Systems Biology*, in «History and Philosophy of the Life Sciences», 29, 2007, pp. 5-32.

6 B. KUSKA, *Beer, Bethesda, and Biology. How 'Genomics' Came into Being*, in «Journal of the National Cancer Institute», 90, 1998, 2, p. 93.

7 R. HOOKE, *Micrographia: or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses*, London, Jo. Martyn, and Ja. Allestry, printers to the Royal Society, 1665, p. 113. For other cell metaphors see R. MAZZOLINI, *Politisch-biologische Analogien im Frühwerk Rudolf Virchows*, Marburg 1988; A. REYNOLDS, *Ernst Haeckel and the theory of the cell state: remarks on the history of a bio-political metaphor*, in «History of Science», 46, 2008, pp. 1-30. How stem cell research is presented in the current scientific and public debate has been sketched by I. HELLSTEN, *Popular Metaphors of Biosciences: Bridges over Time?*, in «Configurations», 16, 2008, pp. 11-32. A quantitative sociological analysis on the use of the term 'stem cell' of the past 10 years has been proposed by L. LEYDESDORFF - I. HELLSTEN, *Metaphors and Diaphors in Science Communication: Mapping the Case of Stem Cell Research*, in «Science Communication», 27, 2005, pp. 64-99.

The English noun 'stem', in Old English *stemn*, derives from the Latin *stāmen* which means 'thread'. It denominates something elongated that connects other parts, for example the main ascending axis of a plant or the trunk, but likewise the tube of a tobacco pipe, or in music notation the vertical line between the note head and the flag. The more functional meaning of 'stem' is contained in its verb form, which is synonymous with 'growing out', 'taking origin', or 'descending'. In this sense it is also used for the main road from which the secondary roads branch, in linguistics for the root of a word from which all suffixes and prefixes have been removed, in heraldry for the main line of descent of a family, or in business for the core of collaborators or customers. Furthermore, 'to stem' can also mean to 'tamp', to 'plug' or to 'hold back' (by damming). Very similarly, the German *stammen* is a synonym for 'deriving' or 'originating', and *Stamm*, having much less different meanings than its English counterpart, usually denominates a tribe or strain or a trunk. Yet *Stammbaum* is rarely translated as 'stem tree' and more often as 'pedigree'.

The German *Stammzelle* was coined in 1868 by Ernst Haeckel (1834-1919), who connected two hitherto distant terms, 'cell' and 'stem'. Nevertheless, the term was easy to understand because, as we shall see, it fitted well into Haeckel's general outline of ontogenetic and phylogenetic development. It was initially translated into English as 'original cell' and after about 1900 as 'stem cell'. Spanish has the expression *célula madre* (mother cell), and since 1874 French has used *cellule-souche*, which stands for 'stub', 'tribe', 'origin', or 'strain'[8]. Still somewhat obscure is the origin of the Italian term. The literal translation *cellula-stipite* had been used for Haeckel's books[9]. It is not clear when and by whom it was then translated into *cellula staminale*. The term appears almost exclusively in the combination of 'stem' and 'cell'. Although *staminale* resembles the German *Stamm*, it stands, like the Old Norse *stafn*, for the rib of a boat. Yet pious Christians may also recall Adam's rib which

[8] E. HAECKEL, *Histoire de la création des êtres organisés d'après les lois naturelles. Conférences scientifiques sur la doctrine de l'évolution en général et celle de Darwin, Goethe et Lamarck en particulier*; traduites de l'allemand par Ch. Letourneau, Paris 1874, p. 366.

[9] E. HAECKEL, *Storia della creazione naturale. Conferenze scientifico-popolari sulla teoria dell'evoluzione in generale e specialmente su quella di Darwin, Goethe e Lamarck*, traduzione sull'ottava edizione tedesca di D. Rosa, Torino 1892, p. 231.

gave birth to Eve. Some etymologists trace the Italian *staminale* from the Latin *stamina*, the stamen, others maintain that it had been directly translated from the English 'stem'. We can find a word that sounds similar in the Italian *stemma*, the heraldic coat of arms or escutcheon, but it seems not to have had any influence.

Today, talk about 'stem cells' is automatically understood as talk about human embryonic stem cells. Yet, during its more than 150 years of history, the term has been used in different contexts, and it has denoted considerably different though not radically different things. It has always maintained its prospective meaning; for it does not mean 'to stem from' (as in tribal or heraldic descent) but 'to be the stem for something growing out of it', something characterized by its future-ness. Today, the term itself is criticized, and some scientists ask whether the term is still adequate or whether it leads research in the wrong direction. Are all the cells today called 'stem cells' sufficiently similar to warrant the same name? Are stem cells specific and distinct enough to merit a proper name, or is stem-ness rather a broader regenerative capacity of tissues? Moreover, the teleological connotation that suggests stemming as an irreversible process is under attack. For these discussions it might be helpful to look at the reasons that induced some of the pioneers of stem cell research to use or not to use the term 'stem cell'.

3. *A botanical prelude – the anatomical stem cell*

Although the term 'meristem' denotes the small apical part of a plant consisting mainly of what we call today 'stem cells', it does not stand behind their etymology. Rather, in 1858 the Swiss botanist Karl Wilhelm von Naegeli (1817-1891) added the suffix '-em' to the Greek *meristos* ('divided', 'dividable') to describe the area of continuous cell division[10]. The plant stem, although consisting of cells, does not lie at the conceptual basis of stem cell research either. And yet there is a surprising correspondence. Every gardener and horticulturist knows the very simple technique of layering: cutting a plant stem and putting it into a suitable medium so that it will readily root at the base and produce leaves at the top. It is not only plant stems that possess this astonishing

[10] M. Ramalho Sanchez - H. Willenbring, *On the Origin of the Term 'Stem Cell'*, in «Cell Stem Cell», 1, 2007, pp. 35-38.

capacity, so too do some other parts. If properly stimulated by injury, one single cell of the epidermis of a *Begonia* leaf, for example, is able to form an adventitious shoot which will grow into a new clone plant. In the very literal sense, in plants an (anatomical) stem cell can become a (functional) stem cell. Despite being of great practical and economic importance, and despite having established a flourishing industry of plant cell culture, until recently this easily manageable form of vegetative propagation has received little scientific interest and has had hardly any connection to (medical) stem cell research. Botany plays almost no role at all in the history of stem cell research. Yet, as we shall see, today it has regained importance.

It was the metaphorical stem that gave birth to the term 'stem cell'. Hence the story starts with a word, not with a discovery, invention, or description. And the metaphor accompanied the subsequent developments even after its original meaning had been forgotten.

4. *The biogenetic stem cell*

Ernst Haeckel, whose search for a unified view of life was mainly influenced by evolutionary biologist Charles Darwin and botanist and cytologist Matthias Schleiden[11], was a master in coining catchy terms. Some were fortunate, like *Ökologie* (ecology), gastrulation, and ontogeny (for the individual development); others less so, for instance *Substanz-Gesetz* (law of substance). Two of his verbal creations are of particular interest here: *Stamm* (phylum, tribe, trunk) and phylogeny (the evolutionary development and relation of organisms or life in general). Both terms have much in common: linguistically because the Greek *phylé* means trunk, stock, and contextually because Haeckel introduced trees as icons of evolutionary branching and of the progression from the basic stem to the crown. At the top of his *Stammbäume* he placed the most evoluted organisms, at the bottom the very first living being and the common ancestor of all successive organisms – the stem cell.

Haeckel's *Natürliche Schöpfungsgeschichte* (1868) is replete with terms like *Stammbaum* (stem tree), *Stammform* (stem form), *Stammeltern*

[11] G. Uschmann, *Ernst Haeckel. Biographie in Briefen mit Erläuterungen*, Leipzig 1984; R.J. Richards, *The Tragic Sense of Life, Ernst Haeckel and the Struggle over Evolutionary Thought*, Chicago - London 2008.

(stem parents), and similar. Thus, he did not need to define or explain anything when he introduced the word *Stammzelle* (stem cell) in chapter 15, *Stammbaum und Geschichte des Protistenreiches*:

«Auf Grund der embryologischen Urkunden können wir also mit voller Sicherheit behaupten, daß alle mehrzelligen Organismen eben so gut wie alle einzelligen ursprünglich von einfachen Zellen abstammen; hieran würde sich sehr natürlich der Schluß reihen, daß die älteste Wurzel des Thier- und Pflanzenreichs gemeinsam ist. Denn die verschiedenen uralten *Stammzellen*, aus denen sich die wenigen verschiedenen Hauptgruppen oder *Stämme* (Phylen) des Thier- und Pflanzenreichs entwickelt haben, könnten ihre Verschiedenheit selbst erst erworben haben, und könnten selbst von einer gemeinsamen *Urstammzelle* abstammen. Wo kommen aber jene wenigen *Stammzellen* oder diese eine *Urstammzelle* her? Zur Beantwortung dieser genealogischen Grundfrage müssen wir auf die früher erörterte Plastidentheorie und die Urzeugungstheorie zurückgreifen» (my emphasis)[12].

The English translation, even in the sixth edition of 1914, did not use the term 'stem cell' nor the singular 'stem'. The chapter is entitled *Pedigree and History of the Kingdom of the Protista* and states:

«Upon the ground of embryological records, therefore, we can with full assurance maintain that all many-celled, as well as single-celled, organisms are originally descended from simple cells; connected with this, of course, is the conclusion that the most ancient root of the animal and vegetable kingdom was common to both. For the different primaeval *original cells* out of which the few different main groups or *tribes* have developed, only acquired their differences after a time, and were descended from a common *primaeval cell*. But where did those few *original cells*, or the one *primaeval cell*, come from? For the answer to this fundamental genealogical question we must return to the theory of plastids and the hypothesis of spontaneous generation which we have already discussed» (my emphasis)[13].

In this way Haeckel linked evolution and cell theory. Yet, he was not a Darwinist as we understand the term today. His Lamarckian idea of the intrinsic causes of evolutionary progress becomes explicit when he specifies how one should imagine the origin of life:

[12] E. HAECKEL, *Natürliche Schöpfungsgeschichte. Gemeinverständliche wissenschaftliche Vorträge über die Entwickelungslehre im Allgemeinen und diejenige von Darwin, Goethe und Lamarck im Besonderen, über die Anwendung derselben auf den Ursprung des Menschen und andere damit zusammenhängende Grundfragen der Naturwissenschaft*, Berlin 1868, p. 322.

[13] E. HAECKEL, *The History of Creation: Or Development of the Earth and Its Inhabitants by the Action of Natural Causes. A Popular Exposition of the Doctrine of Evolution in General, and that of Darwin, Goethe, and Lamarck in Particular*, translation revised by E. Ray Lancaster, 2 vols, New York 1914[6], vol. 2, p. 41.

«For as all trace of organization – all distinction of heterogeneous parts – is still wanting in them [the Monera], and as all the vital phenomena are performed by one and the same homogeneous and formless matter, we can easily imagine their origin by spontaneous generation ... Only such homogeneous organisms as are yet not differentiated, and are similar to inorganic crystals in being homogeneously composed of one single substance, could arise by spontaneous generation, and could become the primaeval parents of all other organisms»[14].

Though it denoted a (hypothetic) phylogenetic entity, Haeckel's stem cell had many things in common with the stem cells of today: namely its being a specific cell distinguished by its undifferentiatedness and its enormous developmental potential.

In his *Anthropogenie* (1874) Haeckel goes further. When he discusses individual development, the term *Stammzelle* appears thirty-six times and performs a role of outstanding importance by linking phylogeny and ontogeny. According to Haeckel, during ontogeny every organism recapitulates its phylogenetic stages, and the ontogenetic stem-cell – the fertilized egg cell – is the corresponding entity of the phylogenetic stem-cell:

«As, however, the original egg-cell has the same structure in the case of Man as in that of all other animals, we may reasonably assume that this *one-celled original form* was probably the common one-celled *ancestral organism* [German: *Stamm-Organismus*] of the whole animal kingdom, including Man» (my emphasis)[15].

Some years later, Joseph McCabe (1867-1955), a former priest who converted to atheism and science popularization[16], published a new translation in which the term 'stem cell' appeared at least forty-two times, and the same statement ran as follows:

[14] *Ibidem*, vol. I, pp. 418-419.

[15] E. HAECKEL, *The Evolution of Man: A Popular Exposition of the Principal Points of Human Ontogeny and Phylogeny*, 2 vols, New York 1879, p. 140. The original version in E. HAECKEL, *Anthropogenie oder Entwicklungsgeschichte des Menschen. Gemeinverständliche wissenschaftliche Vorträge über die Grundzüge der menschlichen Keimes- und Stammes-geschichte*, Leipzig 1874, p. 109: «Da nun aber die ursprüngliche Eizelle beim Menschen und allen Thieren dieselbe einfache Beschaffenheit besitzt, so werden wir auch mit Wahrscheinlichkeit schließen dürfen, dass jene einzellige *Stammform* der gemeinsame einzellige *Stamm-Organismus* für das ganze Thierreich, den Menschen inbegriffen, war» (my emphasis).

[16] B. COOKE, *Joseph McCabe: A Forgotten Early Populariser of Science and Defender of Evolution*, in «Science & Education», 19, 2010, pp. 461-484.

«And as the original ovum in man and all the other animals has the same simple and indefinite appearance, we may assume with some probability that this *unicellular stem-form* was the common ancestor of the whole animal world, including man» (my emphasis)[17].

Likewise, the *Stammzelle* of Haeckel's definition, in 1879 and 1897 still translated as 'parent-cell'[18], is now called 'stem cell':

«With that end, I have given a special name to the new cell from which the child develops, and which is generally loosely called 'the fertilised ovum' or 'the first segmentation sphere'. I call it 'the stem-cell' (*cytula* or *archicytos*), its cell-matter 'the stem-plasm' (*archiplasma* or *cytuloplasma*), and its nucleus 'the stem-nucleus' (*archicaryon* or *cytulocaryon*). The name 'stem-cell' seems to me the simplest and most suitable because all the other cells of the body are derived from it, and because it is, in the strictest sense, the stem-father and stem-mother of all the countless generations of cells of which the multicellular organism is to be composed»[19].

It had probably been the reading of Edmund B. Wilson's *The Cell in Development and Inheritance* (1896), quoted by McCabe in the title of the sixth chapter, that had induced him to change terminology. Yet, as we shall see, Wilson had taken the word and the meaning from Theodor Boveri, not from Haeckel.

Connecting ontogeny and phylogeny, Haeckel ascribed the stem cell a very special status:

«The ovum stands potentially for the entire organism – in other words, it has the faculty of building up out of itself the whole multicellular body. It is the common parent of all the countless generations of cells which form the different tissues of the body; it unites all their powers in itself, though only potentially or in the germ. In complete contrast to this, the neural cell in the brain ... develops along one rigid line. It cannot,

[17] E. HAECKEL, *The Evolution of Man: A Popular Exposition of the Principal Points of Human Ontogeny and Phylogeny*, translated from the Fifth (enlarged) edition by J. McCabe, 2 vols, New York 1905, vol. 1, p. 116.

[18] E.g. E. HAECKEL, *Evolution of Man*, 1879, vol. 1, p. 176; 1897, vol. 1, p. 176.

[19] E. HAECKEL, *Evolution of Man*, 1905, vol. 1, pp. 130-131. This statement is missing in the first German edition, but is part of the third edition: E. HAECKEL, *Anthropogenie*, 1877[3], p. 144: «Ich bezeichne demnach die neue Zelle, aus der eigentlich das Kind hervorgeht und welche gewöhnlich schlechtweg 'die befruchtete Eizelle' oder 'die erste Furchungskugel' genannt wird, mit einem besonderen Namen: als Stammzelle (*Cytula*), und den Kern derselben als Stammkern (*Cytococcus*). Der Name 'Stammzelle' scheint mir deshalb der einfachste und passendste, weil alle übrigen Zellen des Organismus von ihr abstammen und weil sie im eigentlichsten Sinne der Stammvater und zugleich die Stammmutter aller der zahllosen Zellen-Generationen ist, aus denen sich später der vielzellige Organismus zusammensetzt».

like the ovum, beget endless generations of cells, of which some will become skin-cells, others muscle-cells, and others again bone-cells»[20].

Opposing the delicately structured nerve-cell as the most elaborate and final form of all human cells against the egg-cell as having hardly any structure at all but containing the power to create the whole organism, Haeckel stressed the dualism between amorphous genetic potency and the feeble differentiatedness typical of all kinds of epigenetic concepts. Similar Lamarckian statements were resumed in his very popular *Die Welträthsel*[21].

5. *The germ plasm stem cell*

With the early decline of Haeckel's concept of *Monera* and of his biogenetic law, the phylogenetic stem cell disappeared, giving way to the ontogenetic stem cell. Nevertheless, the idea of connecting evolutionary biology, embryology and heredity, ontogeny and phylogeny, and the idea of stem trees and of stem-cells as their basic anatomical entities, remained vivid when, during the last decades of the nineteenth century, decisive steps were taken for a cellular interpretation of development and differentiation.

In 1892 three publications appeared that considerably changed the meaning of stem cell research. The first and most famous was *The Germ Plasm* by evolutionary zoologist August Weismann (1834-1914), a friend of Haeckel[22]. Although this theory never used the term 'stem cell', it

[20] *Ibidem*, vol. 1, pp. 103-104. In German: E. HAECKEL, *Anthropogenie*, 1874, p. 99: «Die Eizelle repräsentirt potentiell das ganze Thier; d.h. sie besitzt die Fähigkeit, aus sich allein den ganzen vielzelligen Thierkörper hervorzubilden; sie ist die gemeinsame Stammmutter aller der Generationen von zahllosen Zellen, die sich zu den verschiedenen Geweben des Thierkörpers ausbilden; sie vereinigt deren verschiedenartige Kräfte in gewissem Sinne in sich, aber nur potentiell, nur der Anlage nach. Im grössten Gegensatze dazu ist die Nervenzelle des Gehirns (Fig. 2) höchst einseitig ausgebildet. Sie vermag nicht gleich der Eizelle zahlreiche Zellen-Generationen zu erzeugen, von denen sich die einen zu Hautzellen, die anderen zu Fleischzellen, die dritten zu Knochenzellen u.s.w. umbilden».

[21] E. HAECKEL, *Die Welträthsel. Gemeinverständliche Studien über Monistische Philosophie*, Bonn 1899, p. 58; E. HAECKEL, *The Riddle of the Universe at the Close of the Nineteenth Century*, translated by J. McCabe, New York - London 1901, p. 63.

[22] A. WEISMANN, *Das Keimplasma: eine Theorie der Vererbung*, Jena 1892.

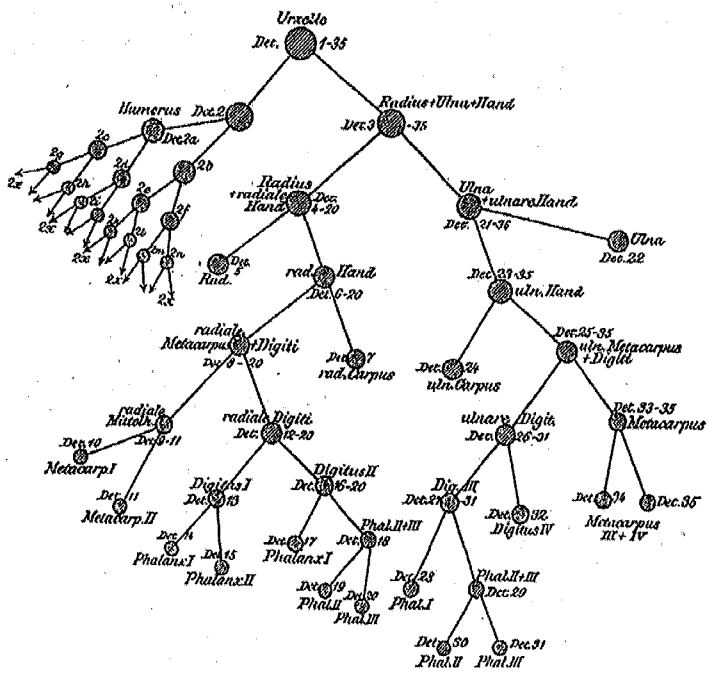
had far-reaching implications for the conception of cell differentiation. Even if many aspects were heavily criticised and scarcely confirmed by future experimental research, they exerted great influence on the following generation of embryologists, experimental geneticists and evolutionary biologists[23]. Weismann asserted a continuity of the germ plasm cells during the development of an organism (intra-generational germline), and he maintained that only this germ plasm was transmitted to the next generation (inter-generational germline). He saw heredity as the transmission of material particles possessing a precise internal hierarchical structure and located in the nucleus. The most fundamental though invisible 'biophores' – molecules that were the bearers of vitality, of the power of growth and multiplication – built up the 'determinants' which directed development and operations. The determinants were assembled in *ids*, complete sets of individual ancestral germ-plasms, and these were stored in *idants*, later identified with the chromosomes. Only the germ cells possessed a complete set of determinants, whereas their distribution in somatic cells was qualitatively different because it had undergone a progressive sequestration of the determinants (fig. 1). In this way differentiation became a teleonomic process of progressive restriction of the number of determinants and thus of potency.

Stimulated by this model, many embryologists started research projects to follow every cell division from the fertilized egg to the stage of gastrulation in order to unravel the cell lineage of certain organisms; and some embryologists set out to find these special germ cells in order to confirm or confute Weismann's ideas. One of them was Weismann's assistant Valentin Haecker (1864-1927), later professor at Stuttgart and Halle. In 1892 he investigated the initial cleavage stages of *Cyclops* and observed an unequal cell division with one big cell migrating into the center of the embryo (fig. 2). He called this cell which gave rise by division to both germ cells and somatic cells the 'stem cell': «One cell ... enters the central part of the egg: this is the common stem cell of the primeval mesoderm cells and the primeval germ cells»[24].

[23] R.G. WINTHER, *August Weismann on Germ-plasm Variation*, in «Journal of the History of Biology», 34, 2001, pp. 517-555.

[24] V. HAECKER, *Die Kerntheilungsvorgänge bei der Mesoderm- und Entodermbildung von Cyclops*, in «Archiv für mikroskopische Anatomie», 39, 1892, pp. 556-581, here p. 559.

Figure 1. *August Weismann's concept of the segregation of the determinants during differentiation illustrated with the development of the hand*



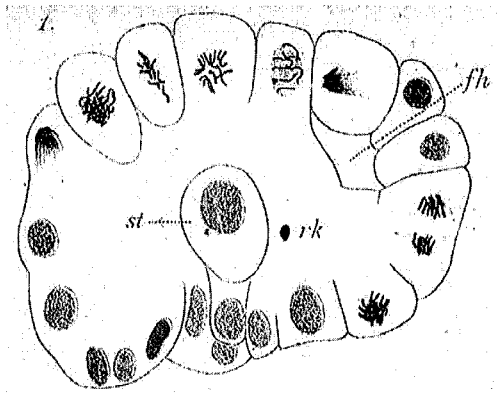
The *Urzelle* (primordial cell) at the top contains the determinants 1-35 which are then progressively divided up.

Source: E. WEISMANN, *Das Keimplasma*, 1892, p. 135.

More important than Haecker's work was Theodor Boveri's (1862-1915) paper on the embryology of *Ascaris* (today *Parascaris*). Resuming a study started five years before[25], Boveri noted that during the first cleavage stages the chromatin content of some cells was visibly reduced. Convinced that he had an empirical proof for Weismann's theory, he felt authorized to name these cells 'stem cells':

[25] T. BOVERI, *Ueber Differenzierung der Zellkerne während der Furchung des Eies von Ascaris megalocephala*, in «Anatomischer Anzeiger», 2, 1887, pp. 688-693. Here he explicitly refers to Weismann's germ plasm theory but never uses the word stem cell.

Figure 2. *Valentin Haecker's illustration of the initial cleavage stages of «Cyclops»*



Haecker's stem cell is the big cell in the center of the embryo of *Cyclops*.
Source: V. HAECKER, *Die Kerntheilungsvorgänge*, 1892, Tav. XXIV, fig. 4.

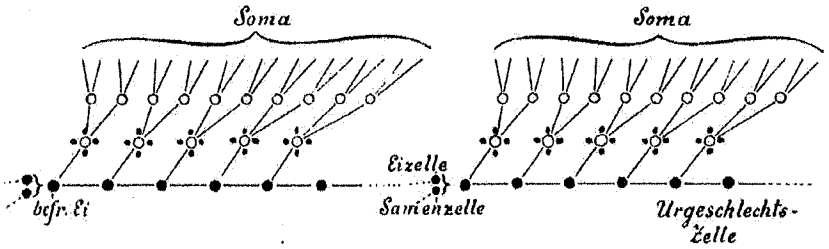
«Maybe one could appropriately denote the cells which lead through a simple series from the fertilized egg-cell to the original germ cell and which maintain the character of the egg in their chromatin with the name 'stem cell', proposed by Haeckel for the fertilized egg, and, on the other hand, the 5 cells which branch off from this stem line and lead to the soma with the name 'somatic ancestral cells' or 'ancestral soma cells'»[26].

However, Boveri did not observe a similar reduction in the further differentiation of the somatic cells. Here, the chromatin seemed to remain equal. Boveri illustrated his concept by sketching a diagram of a *Zellen-Stammbaum*, a cell-stem tree (fig. 3).

It was in this sense that the 'stem cell' was introduced into the Anglo-Saxon terminology. In his famous textbook *The Cell in Development*

[26] T. BOVERI, *Über die Entstehung des Gegensatzes zwischen den Geschlechtszellen und die somatischen Zellen bei Ascaris megalocephela*, in «Sitzungsberichte der Gesellschaft für Morphologie und Physiologie», 8, 1892, pp. 114-125, here p. 117: «Man könnte die Zellen, welche in einfacher Reihe vom befruchteten Ei zur Urgeschlechtszelle hinführen, und die den Charakter des Eies in ihrem Chromatin bewahren, vielleicht passender Weise mit einem von Haeckel für das befruchtete Ei vorgeschlagenen Namen als 'Stammzellen' bezeichnen, die 5 Zellen dagegen, welche von dieser Stammlinie abzweigen und zur Entstehung des Soma führen, als 'somatische Urzellen' oder 'Ursomazellen'».

Figure 3. *Boveri's cell-stem tree*



The black circle stands for a cell possessing the original two chromosomes, the white circle for a cell having a reduced nucleus, and the white circle with four dots for a cell in which the chromatin reduction is taking place. 'befr. Ei' = fertilized egg; 'Eizelle' = egg cell; 'Samenzelle' = sperm cell; 'Urgeschlechtszelle' = ancestral germ cell'.

Source: T. BOVERI, *Entstehung des Gegensatzes*, 1892, p. 118, fig. 1.

and Inheritance Edmund B. Wilson (1856-1939) talked about stem cells when discussing the works of Haecker and his close friend Boveri[27].

Interestingly, he also used the word 'stem' when presenting the studies on regeneration carried out by Jacques Loeb (1859-1924), Hans Driesch (1867-1941), Elisabeth E. Bickford (1861-1939), and Thomas H. Morgan (1866-1945) (see below); yet he did not use it in the ontogenetic-cellular sense but in the mere anatomical one[28]. This is even more surprising upon reading a few lines later an astonishing statement on the regenerative power of these animals:

«Nevertheless the facts of regeneration prove that even in the adult the formative processes in special parts are in many cases definitely correlated with the organization of the entire mass; and there is reason to conclude that such a correlation is a survival, in the adult, of a condition characteristic of the embryonic stages, and that the independence of special parts in the adult is a secondary result of development»[29].

[27] E.B. WILSON, *The Cell in Development and Inheritance*, New York 1896, pp. 110-113; nearly identical is E.B. WILSON, *The Cell in Development and Inheritance*, New York 1900^2, pp. 146-149.

[28] E.B. WILSON, *The Cell*, 1900^2, pp. 392-393.

[29] *Ibidem*, p. 394; very similar in E.B. WILSON, *The Cell*, 1896, p. 294.

At around the turn of the century, even those researchers engaged in both fields of investigation did not consider the phenomenon of embryonic differentiation and the phenomenon of regeneration conceptually similar enough to denote them with the same terminology.

Nevertheless, also in its ontogenetic sense, the term 'stem cell' enjoyed only limited success. Initially, Wilhelm Roux's (1850-1924) famous experiments with frog embryos seemed to furnish the most powerful support for Weismann's concept of cellular differentiation. Notably, Roux first excluded the influence of external factors like mechanical pressure or gravity by continuously rotating the developing eggs and obtaining normal organisms. In a second series of experiments conducted in 1888, he punctured one cell of the two-celled embryos with a hot needle and obtained half-embryos. Both results induced him to consider development as due to inherited internal structural factors which are progressively segregated from the very first cell division onwards, forming qualitatively different cells and thus causing an irreversible ontogenetic determination. A few years later Hans Driesch repeated Roux's experiments with sea urchin eggs, obtaining smaller but normally formed embryos. The remaining cell had been able to compensate for the missing material. Driesch proposed a more holistic view of regulative forces acting on the whole organism. Studies on cell lineage, too, evidenced that it was still possible to experimentally modify the single parts of the embryo. Only after gastrulation were the fates of the single cells and layers definitely determined.

Nor were Boveri's results confirmed, however. His observations were correct, and they represent one of the first attempts to connect chromosomal behavior to heredity. During the initial division stages, the chromosomes in *Ascaris* remain indeed intact in germ-line cells but they shatter in somatic cell lines. However, as Richard Burian has shown, Boveri's research organism was unluckily chosen because it showed a very particular phenomenon that could not be generalized[30].

These results were among the factors that contributed to the decline of the early projects of cell lineage. These were no longer considered helpful for the discussion on mechanical versus intrinsic causes of de-

[30] R. BURIAN, *How the Choice of Experimental Organism Matters: Epistemological Reflections on an Aspect of Biological Practice*, in «Journal of the History of Biology», 26, 1993, pp. 351-367, here pp. 352-353.

velopment[31]. This also stopped Boverian attempts to identify the stem cells of ontogenesis. Although they continued to be propagated in the last editions of Wilson's textbook[32], the term and the concept had little influence on developmental research. Nevertheless, the Roux-Driesch debate indirectly made some fundamental contributions to stem cell research: 1. the new experimental settings, namely the techniques of manipulation of cleavage cells and Roux's tools which enabled observation of living egg-cells in culture (see below), and 2. fundamental concepts such as that of totipotency, i.e. the ability to respond to the needs of the whole and to become any part of the whole that the conditions demanded, of *prospektive Bedeutung* (prospective value or significance) and *prospektive Potenz* (prospective potency), and the distinction between 'real' fate and 'possible' fate[33].

6. *The hematopoietic stem cell*

The term and the concept of 'stem cell' survived in a seemingly distant field: hematology. In the late nineteenth century the study of blood, too, was linked to cell theory. As soon as it became obvious that blood and bone marrow consisted of different cell types, questions about their origin arose. One of the early protagonists of such inquiry was Arthur Pappenheim (1870-1916), who started studying philosophy at Freiburg, Weismann's university, and then switched to medicine in Berlin. In 1895 Rudolf Virchow (1821-1902) supervised his dissertation on the cellular composition of the bone marrow. Applying cell theory and Virchow's concept of cellular pathology to hematology and leukemia, Pappenheim devoted himself to the question of the origin and genetic relationship of the single constituents. Like Virchow, Pappenheim supported the unitarian concept of the origin of blood cells, contrary to the dualistic view that assumed two distinct lines. In this context of the first years

[31] R. GURALNICK, *A Recapitulation of the Rise and Fall of the Cell Lineage Research Program: The Evolutionary-developmental Relationship of Cleavage to Homology, Body Plans and Life History*, in «Journal of the History of Biology», 35, 2002, pp. 537-567.

[32] E.g. E.B. WILSON, *The Cell in Development and Heredity*, New York 1925[3], fig. 125 and pp. 310-327; and 1937[3], *ibidem*.

[33] H. DRIESCH, *The Science and Philosophy of the Organism. Gifford Lectures Delivered at Aberdeen University*, 2 vols., London 1908.

of the twentieth century the term 'stem cell' acquired a central role by representing for both sides the genetic origin of blood cells. The discussion revolved around the question of which cell type represented the stem cell and whether there was one line or two distinct ones. Hence, once again, the story starts with a word which stood for a rather generic and hypothetic entity. Yet all researchers were confident that it would soon be replaced by a concrete one.

Many hematologists of the time illustrated their theories with blood cell stem trees. Probably the first one was published in 1904 by Viennese hematologist and dualist Wilhelm Türk (1871-1916)[34]. Pappenheim sketched twenty-one increasingly complex pedigrees of blood cells[35]. Among them was a 1905 graph entitled «Ausgang und Stammzelle» (origin and stem-cell). Contrary to other scholars who only made use of words, Pappenheim preferred symbols (fig. 4)[36] which strongly resembled those of Weismann (fig. 1) and Boveri (fig. 3).

In around 1910, 'stem cell' was a term current among hematologists, as testified by the contributions of Ernst Neumann (1834-1918)[37] and Russian Alexander A. Maximov (1874-1928). In some historical reviews both are called founders of the hematopoietic stem cell concept[38]. In 1908 Maximov gave a speech at the congress of the Hematological Society in Berlin titled *The Lymphocyte as a Stem Cell Common to Different Blood Elements in Embryonic Development and during the*

[34] W. Türk, *Vorlesungen über klinische Hämatologie*, vol. 1, Wien - Leipzig 1904, pp. 335 and 401.

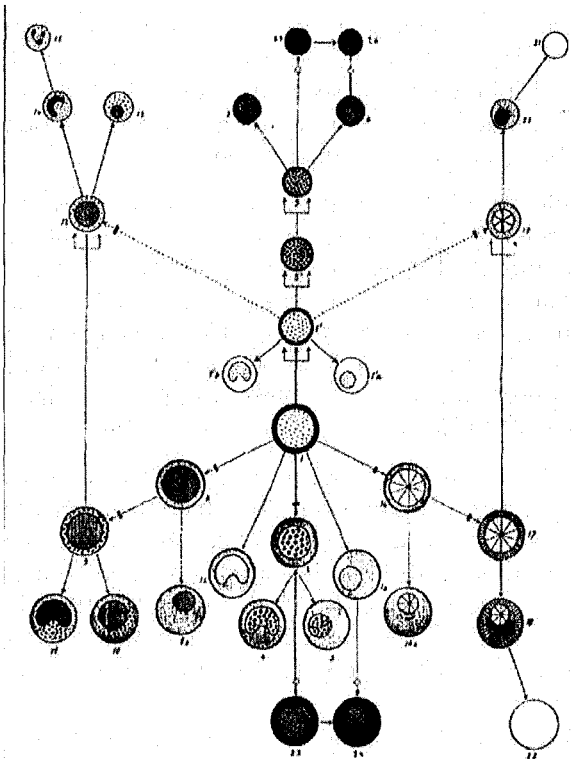
[35] R. Dinser, *Der Beitrag Artur Pappenheims zur Hämatologie um die Jahrhundertwende*, PhD Dissertation Universität Bochum, 2001.

[36] A. Pappenheim, *Bemerkungen über artliche Unterschiede und die gegenseitigen genetischen Beziehungen zwischen den verschiedenen lymphoiden Zellformen des Blutes*, in «Folia haematologica», 9, 1905, pp. 321-404.

[37] E. Neumann, *Hämatologische Studien III: Leukozyten und Leukämie*, in «Virchows Archiv», 207, 1912, pp. 279-412.

[38] See e.g. A. Friedenstein, *Stromal-hematopoietic Interrelationships: Maximov's Ideas and Modern Models*, in R. Neth (ed.), *Modern Trends in Human Leukemia*, Berlin - Heidelberg 1989, vol. 8, pp. 159-167; N.H. Zech - A. Shkumatov - S. Koestenbauer, *The Magic Behind Stem Cells*, in «Journal of Assisted Reproduction and Genetics», 24, 2007, 6, pp. 208-214; A.A. Novik et al., *The Maximov 1909 Centenary: A Reappraisal*, in «Cellular therapy and transplantation», 1, 2009, 1, doi: 10.3205/ctt-2009-en-000034.01, on: http://ctt-journal.com/1-3-en-novik-et-al-2009may25.html (accessed 24th November 2010).

Figure 4. *Pappenheim's blood cell pedigree*



The big circle in the center of the graph with a thick black line represents the 'big lymphocyte' from which all other cell types originate.

Source: A. PAPPENHEIM, *Bemerkungen über artliche Unterschiede*, 1905, p. 347.

Post-fetal Life of Mammals[39]. However, at no place in his paper except in the title did he use the expression 'stem cell'.

Whereas the ontogenetic stem cell concept encountered its main obstacle in the difficulty of tracing a distinct germ cell line between the progenitor cell and its derivates, the hematopoietic stem cell fitted perfectly with

[39] A. MAXIMOV, *Der Lymphozyt als gemeinsame Stammzelle der verschiedenen Blutelemente in der embryonalen Entwicklung und im postfetalen Leben der Säugetiere*, in «Folia Haematologica», 8, 1909, pp. 125-134.

the idea of ontogenetic stems and with the concepts of Weismannian cell fate and progressive and irreversible restriction of potency – as testified also by its introduction into mammalian leukemia research in 1949[40]. Contrary to ontogeny, the term 'stem cell' was well established in hematology. To talk about stem cells was now to talk about hematopoietic stem cells (HSC). Yet once again things were not so simple. As it moved into hematology, the term 'stem cell' retained large part of its original meaning. However, some important aspects changed:

1. Stem cells were now 'adult' stem cells whose function and potency were much more restricted: namely to the production of different blood cells. This phenomenon was called pluripotency. On the other hand, contrary to embryonic stem cells, this capacity continued throughout the entire lifetime of the organism.

2. Moving away from biology and into medicine, stem cell research focused on the capacity for self-renewal and self-repair, thus becoming a promising field of clinical cancer therapies, and from the 1990s also of regenerative medicine. Although unexpected drawbacks constantly forced it back to basic research, from the 1960s onwards the hematopoietic stem cell represented an important clinical field able to benefit from close collaboration with hospitals and with powerful institutional settings like blood banks[41]. The stem cell aroused growing practical expectations and became synonymous with bone marrow transplantation and cancer, and in the 1980s with hematopoietic stem cell transplantation (HSCT)[42]. Owing to this 'regime of hope', it received investments, institutions and networks of its own, and it became a research field in its own right.

3. The unitarism-dualism debate was not settled owing to the impossibility of clearly distinguishing the morphology of the different cell

[40] T.S. Evans - A.P. Cipriano - E.H. Ferrell Jr., *Reticulo-endotheliosis or Stem-Cell Leukemia: A Case Report*, in «Connecticut State Medical Journal», 13, 1949, 12, pp. 1128-1133.

[41] N. Brown - P. Martin - A. Kraft, *The Promissory Pasts of Blood Stem Cells*, in «BioSocieties», 1, 2006, pp. 329-348; M.B. Fagan, *The Search for the Hematopoietic Stem Cell: Social Interaction and Epistemic Success in Immunology*, in «Studies in the History and Philosophy of Biology and the Biomedical Sciences», 38, 2007, pp. 217-237.

[42] P. Martin - N. Brown - A. Kraft, *From Bedside to Bench? Communities of Promise, Translational Research and the Making of Blood Stem Cells*, in «Science as Culture», 17, 2008, pp. 29-41.

types, especially during their early stages. Whereas the first decades of the history of stem cell research were characterized by the conviction that it was possible to distinguish stem cells morphologically (for Haecker stem cells were bigger, for Boveri they contained band-shaped chromosomes, and Pappenheim devoted most of his energies to finding a specific staining technique and a method for the quantitative analysis of the chromatin content of stem cells[43]) hematologists became increasingly aware of the insufficiency of these traditional criteria[44]. Stem cells were now defined not in terms of shape or topography but in terms of function, namely their extensive proliferation and their double capacity for extensive proliferation, differentiation 'and' self-renewal.

4. The impossibility of morphologically defining a stem cell led to conceptual and experimental innovations. In 1914, Alexander Maximov implemented his hematological work through use of the recently devised techniques of cell and tissue culture (see below). Yet, on observing bone marrow fibroblasts in hanging-drop cultures, he became aware that not only intrinsic factors were at work, and he consequently proposed his theory of the local differentiation conditions operating in hematopoiesis. This concept – today resumed in the study of the hematopoietic microenvironment[45] – was initially received with great skepticism because, as we shall see in the next section, it represented a further considerable shift in the definition of stem cells and their function. Another crucial technology, the CD34 antigene surface marker which selectively adheres to the surface of hematopoietic stem cells, was introduced in 1984 by child oncologist Curt Civin. Yet, the hope of finally being able to distinguish the stem cells clearly from the rest of the marrow cells and thus have a technique with which to identify, isolate, collect and handle this precious object was disappointed when CD34 turned out to be less specific, and 'normal' cells proved to be much more plastic than thought.

5. Notwithstanding all the drawbacks, stem cells were transformed into objects of manipulation and ultimately also into commodities on the

[43] R. DINSER, *Pappenheim*, pp. 47-51.

[44] P. TRIADOU, *The History of the Hematopoietic Stem Cell Concept*, in C. GALPERIN - S.F. GILBERT - B. HOPPE, *Fundamental Changes in Cellular Biology in the 20th Century*, Turnhout 1999, pp. 143-149.

[45] A. FRIEDENSTEIN, *Stromal-hematopoietic Interrelationships.*

growing market of bioeconomics[46]. These projects, too, were designed mainly in hematopoietic stem cell systems. Key events were the invention in 1961 by biophysicist James Till and physician Ernest McCulloch's device of the first functional assay method in radiated mice, and twenty three years later, Civin's already mentioned surface marker. Although these two methods did not resolve all problems, they contributed greatly to the better identification of stem cells, their extraction, and their use in tissue engineering. Interestingly, only when they had a means to 'handle', i.e. transplant, stem cells, did many researchers become convinced that stem cells really exist[47].

7. *The cultured stem cell*

It is one of the paradoxes of the history of the life sciences that many biological entities escape at the very moment that they finally seem to be in the hands of researchers. Probably the best known example is the 'gene'[48]. A similar case is the 'stem cell'. In parallel with increasing confidence in being close to the unification of the theoretical entity 'stem cell' and its supposed ontological counterpart, scientists encountered increasing difficulties in locating the extraordinary regenerative power in one or few distinct and identifiable cells. Still today, one of the main tasks of the International Stem Cell Initiative (ISCI) is to generate a standard design of 'the' stem cell[49], and a growing number of scientists suggest that the present-day concept of 'stem cell' should be profoundly rethought[50].

[46] N. BROWN - P. MARTIN - A. KRAFT, *The Promissory Pasts of Blood Stem Cells*, pp. 330-331.

[47] A version propagated by Till and McCulloch themselves on the webpage of the Canada Science and Technology Museum) http://www.sciencetech.technomuses.ca/english/about/hallfame/u_i46_e.cfm

[48] See e.g. H.-J. RHEINBERGER - S. MÜLLER-WILLE, *Gene Concepts*, in S. SARKAR - A. PLUTYNSKI (eds), *A Companion to the Philosophy of Biology*, Oxford 2008, pp. 3-21.

[49] L. ERIKSSON - A. WEBSTER, *Standardizing the Unknown: Practicable Pluripotency as Doable Futures*, in «Science as Culture», 17, 2008, pp. 57-68.

[50] See e.g. H.M. BLAU - T.R. BRAZELTON - J.M. WEIMANN, *The Evolving Concept of a Stem Cell: Entity or Function?*, in «Cell», 105, 2001, p. 829; D. ZIPORI, *The Nature of*

Both processes, convergence as well as divergence, are well exemplified in one and the same experimental tool: cell and tissue culture. As stressed by Rheinberger, cell cultures pose a double challenge: conceptual, i.e. the question if vital phenomena can be reproduced with equal value in a Petri dish, and technical, i.e. the creation of proper environments in order to permit the cells or tissues to survive and perform their functions as normally as possible[51]. To succeed, it was of primary importance to prepare the right nutrient solution, to keep the right temperature, and to work under aseptic conditions.

It is impossible to locate the historical origin of tissue cultures exactly. Efforts to keep separate animal organs alive characterized experimental physiology at least from the mid-eighteenth century onwards. Dividing cleavage stages were observed since the 1820s[52], and a pioneering attempt to isolate fragments of these initial stages and observe their activities in a sugar solution was made by Robert Remak in 1855, followed independently by numerous other embryologists and some physiologists. Even Ernst Haeckel, although he was not successful, appears in this list[53]. In 1885 the embryologist and ingenious experimentalist Wilhelm Roux removed small parts of the medullary plate from chicken embryos and maintained them in a warm saline solution for several days. Similar experiences were then reported in regard to frog lymphocytes and even human skin[54]. In 1902 botanist Gottlieb Haberlandt (1854-1945) succeeded in similar pioneering experimentation using mature plant cells, but did not pursue these studies further[55].

Stem Cells: State Rather than Entity, in «Nature Reviews Genetics», 5, 2004, pp. 873-878; A.D. LANDER, *The 'Stem Cell' Concept: Is it Holding us Back?*, in «Journal of Biology», 8, 2009.

[51] H.-J. RHEINBERGER, *Kulturen des Experiments*, in «Berichte zur Wissenschaftsgeschichte», 30, 2007, pp. 135-144, here pp. 138-141.

[52] M. RUSCONI, *Développement de la grenouille commune depuis le moment de sa naissance jusq'à son état parfait*, Milan 1826.

[53] J.M. OPPENHEIMER, *Taking Things Apart and Putting them Together Again*, in «Bulletin of the History of Medicine», 52, 1978, 2, pp. 149-162.

[54] S.P. LANGDON, *Basic Principles of Cancer Cell Culture*, in S.P. LANGDON (ed.), *Cancer Cell Culture. Methods and Protocols*, Totowa NJ 2004, pp. 3-16.

[55] G. HABERLANDT, *Culturversuche mit isolierten Pflanzenzellen*, in «Sitzungsberichte der Mathematisch-Naturwissenschaftlichen Classe der Kaiserlichen Akademie der Wissen-

A qualitative jump was achieved in 1907 when Ross Granville Harrison (1870-1959) sought to break the deadlock in the great debate between neuronists and reticularists[56]. In order to see whether nerve fibers grow out of single cells or whether they are the product of the entire nerve context, Harrison devised a technique which enabled him to observe the behavior of individual nerve cells. Although Harrison was an embryologist and was familiar with Haberlandt's work, he drew inspiration from the 'hanging drop' preparation elaborated in 1880 by bacteriologist Robert Koch (1843-1910). Harrison placed fragments of embryonic frog tissue in a drop of frog lymph on a cover slip. Upon clotting of the lymph, he inverted the slip, put it onto a hollow glass slide and sealed it with paraffin. He was thus able not only to keep the cells alive for a while but also to have them grow, so that he could observe the outgrow from the explants.

The great heuristic value of this technique was not immediately recognized, however. The opponents mostly doubted whether the culture conditions were normal enough to represent real-life phenomena. One of the few scientists to realize the potential of Harrison's technique was Alexis Carrel (1873-1944), who coined the term 'tissue culture' in 1911. Together with Montrose Burrows (1884-1947) he modified Harrison's method, rendering it more easily applicable, and adapted it to other research fields like cancer research and immunology. Of greatest importance were the further prolongation of the life span of these culture cells – Carrel's famous immortal chicken heart 'lived' from 1912 to 1946 – and the development of subculturing, i.e. the creation of infinite new cell lines from an already existing one[57].

With cell culturing, a methodology was developed which is today considered essential for stem cell research, if not for present-day experimental life sciences and biotechnologies in general. Indeed, the three

schaften zu Wien», 111, 1. Abt., 1902, pp. 69-91; G. HABERLANDT, *Experiments on the Culture of Isolated Plant Cells*, in «Botanical Review», 35, 1969, pp. 68-85. See also M. LAIMER - W. RÜCKER (eds), *Plant Tissue Culture. 100 Years since Gottlieb Haberlandt*, Wien 2003.

[56] H. LANDECKER, *New Times for Biology: Nerve Cultures and the Advent of Cellular Life in vitro*, in «Studies in the History and Philosophy of Biology and the Biomedical Sciences», 33, 2002, pp. 667-694.

[57] H. LANDECKER, *Culturing Life. How Cells Became Technologies*, Cambridge MA - London 2007, pp. 47-55.

events today regarded as crucial were all fundamental in adapting cell culture techniques to the needs of stem cell research[58]. However, even more relevant to our interest here in terminology is the way in which cell culturing changed the meaning of stem cells. The first hints that cells might need more than internal determinants to perform their stem cell role in tissues and multicellular organisms came, as seen, from Maximov, and especially from his last contribution on the formation of fibroblasts in plasma-clot cultures of guinea-pig blood cells[59]. It was in the context of cell cultures, especially when combined with cancer research, that the difficulty of controlling and channelling the potency of stem cells emerged. The powerful cell behaved capriciously, and the challenge was not to activate it but rather to make it become what it should. The insight that different tissues and different species needed different cultures, confirming results of the transplantation experiments conducted around 1900; and, more recently, the discovery that embryonic stem cells need to be kept in a Petri dish to maintain their state of permanent, inexhaustible undifferentiatedness, revealed that more than inherent structural factors were at work. Culturing stem cells confirmed Haeckel's intuition of the connection among intrinsic developmental power and amorphousness: the retention of maximum potency is only possible at the cost of not becoming form. Yet the understanding of stem cells as definite, isolatable entities which evolve predictably was severely undermined.

8. *The regeneration stem cell*

The Nobel Prize-winning surgeon Carrel had been mainly interested in wound healing: for example, in the early 1930s he devised the perfusion pump used to keep organs alive outside the body. While also laying the foundations for therapies based on tissue regeneration, the phenomenon of self-renewal, and thus regeneration biology, gained

[58] G.R. MARTIN, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, in «Proceedings of the National Academy of Science», 78, 1981, 12, pp. 7634-7638; M. EVANS - M. KAUFMAN, *Establishment in Culture of Pluri-potential Cells from Mouse Embryos*, in «Nature», 292, 1981, 5819, pp. 154-156; J.A. THOMPSON et al., *Embryonic Stem Cell Lines*.

[59] A. MAXIMOV, *Cultures of Blood Leucocytes. From Leucocyte and Monocyte to Connective Tissue*, in «Archiv für experimentelle Zellforschung», 5, 1928, pp. 169-178.

enormous medical importance and finally linked regeneration and stem cell research together. The struggles over patents, markets, funds, and public support, however, had overemphasized the conceptualization of stem cells as human hematopoietic stem cells, omitting all other phenomena that could or should have been included. Yet the discovery of a still increasing number of different tissue-specific types of stem cells recalled some of the 'forgotten roots' of stem cell research, most of all regeneration research. The notion of the regenerative power of living matter has very remote origins. The legendary stories of Hercules' fight against Hydra or Prometheus' punishment of being bound to a rock where every day an eagle pecked his liver, which eternally regenerated itself to be eaten again, show that the phenomenon was known in antiquity. Most historians locate the beginning of its scientific investigation in the studies by René-Antoine Ferchault de Réaumur (1683-1757) and Abraham Trembley (1710-1784)[60]. As early as 1712 Réaumur reported to the Académie Royal des Sciences de Paris on the regeneration of the claws of crabs, lobster and crayfish. Even more astonishing were Trembley's observations of 1740 on a tiny organism that he had found in a pond near his house and which challenged nearly all the theses of natural philosophy of his time[61]. He called it a 'freshwater polyp', later it was called *Hydra* because of its capacity to regenerate the entire body even if cut into little fragments. Trembley, indeed, felt like Hercules when he created a polyp with seven heads, cut them off and saw them re-grow[62]. These and the numerous subsequent reports and experiments with other animals were strongly linked with the debate on epigenesis, and from the late nineteenth century onwards with embryology[63].

[60] C.E. DINSMORE (ed.), *A History of Regeneration Research. Milestones in the Evolution of a Science*, Cambridge 1991.

[61] I. JAHN, *Biologiegeschichtlicher Kommentar zum Gedicht über den Süßwasserpolypen und die Entstehung des Lebensbegriffes im 18. Jahrhundert*, in H. QUERNER - I. JAHN, *Christoph Gottfried Jacobi und die Süßwasserpolypen des Abraham Trembley*, Marburg a.d.L. 2003, pp. 31-61.

[62] V.P. DAWSON, *Nature's Enigma. The Problem of the Ppolyp in the Letters of Bonnet, Trembley, and Réaumur*, Philadelphia PA 1987, p. 164.

[63] M. COOPER, *Rediscovering the Immortal Hydra: Stem Cells and the Question of Epigenesis*, in «Configurations», 11, 2003, 1, pp. 1-26.

It was Johann Friedrich Blumenbach (1752-1840) who drew an analogy between the regenerative power of the 'green tentacled polyp' and the process of wound-healing in humans suffering from tuberculous dactylitis[64]. He considered both phenomena expressions of one single life-long formative drive (*nisus formativus*; *Bildungstrieb*) acting throughout the whole body:

«A truth which one should never lose sight of during all these investigations ... that generation, nutrition, and regeneration are basically simple modifications of one and the same force which in the first case constructs, in the other maintains, in the third repairs! In other words: nutrition is a general but imperceptibly continuous generation, reproduction on the other hand a repeated but only partial generation. Insight into one of these three would reliably enlighten also the other two»[65].

Some of Blumenbach's statements strongly recall the stem cell debate:

«The whole tentacled polyp consists of numerous completely equal gland-like granules which are connected with each other through a common jelly. This simple stuff is able and available to reconstitute every lost limb»[66].

About a hundred years later, when regeneration biology was linked with cell theory, none of the main participants in the debate spoke of stem cells. Although the phenomenon of regeneration is today one of the pillars of stem cell research, until very recently the cells considered responsible for the renewal were not named so in regeneration studies. In 1872 Nikolaus Kleinenberg (1842-1897) called the responsible cells *interstitielle Zellen*, whereas Jacques Loeb working on tubularian hydroids (1891), Hans Driesch on the gastrula of *Sphaerecchinus* (1894-95), Elisabeth E. Bickford (1861-1939) on *Tubularia* (1894), and

[64] J.F. BLUMENBACH, *Über den Bildungstrieb (nisus formativus) und seinen Einfluß auf die Generation und Reproduktion*, in «Göttingesches Magazin der Wissenschaft und Litteratur», 1, 1780, 5, pp. 247-266, here pp. 247-249.

[65] *Ibidem*, p. 252: «Eine Wahrheit, die man bey allen diesen Untersuchungen nie aus den Augen verlieren darf ... daß schlechterdings Zeugung, Ernährung und Wiederersetzung im Grunde blosse Modifikationen einer und eben derselben Kraft sind, die im ersten Fall baut, im andern unterhält, im dritten repariert! Mit anderen Worten: Nutrition ist eine allgemeine, aber unmerklich continuirte –, Reproduktion hingegen, eine wiederholte aber nur partielle Generation. Ein Licht über eine von diesen dreyen verbreitet, würde zuverlässig auch die anderen beiden zugleich erhellen».

[66] *Ibidem*, p. 262: «Der ganze Armpolyp besteht durchgehend aus lauter völlig gleichen drüsenartigen Kügelchen, die durch eine gemeinschaftliche Gallerte mit einander verbunden sind. Dieser einfache Stoff ist also zur Ergänzung eines jeden verlohrnen Gliedes geschickt, und vorräthig».

Thomas H. Morgan on *Planaria* (1898) did not coin special terms[67]. Warranting a especial mention is Harriet Randolph (1856-1927). Assistant to Morgan, and a friend of Wilson, Loeb and Bickford[68], in 1892 Randolph completed her doctoral thesis on *The Regeneration of the Tail in Lumbriculus*. Separating the worm into two parts, she saw that the circular muscle and the wall of the dorsal blood vessels arose from the great mass of the mesoderm. The ventral mesentery, instead, appeared to originate from one specific cell type (fig. 5):

«[t]hese cells, which I propose to call neoblasts, are distinguishable from the cells of the peritonaeum by their great size and by the presence of a cell body ... The neoblasts are to be regarded as specialized embryonic cells set apart for the rapid formation of new mesodermic tissue»[69].

Several contemporary histologists had described similar phenomena, and some had also noted the analogy with embryonic potency. Yet, Randolph was the first to exactly locate it and to name these cells. She identified neoblasts also in *Tubifex*, where they were even better marked, and in *Chaetogaster*, where they were called 'peritoneal cells'. She continued:

«It has been suggested to me by Professor E.B. Wilson that the neoblasts are comparable to ova. That unlike ova they give rise only to mesoderm seems to me not out of harmony with this conception ... They may represent the ova of the primitive worm which were originally produced in every somite, but which have ceased to develop in any except a few of the segments of the anterior region of the body»[70].

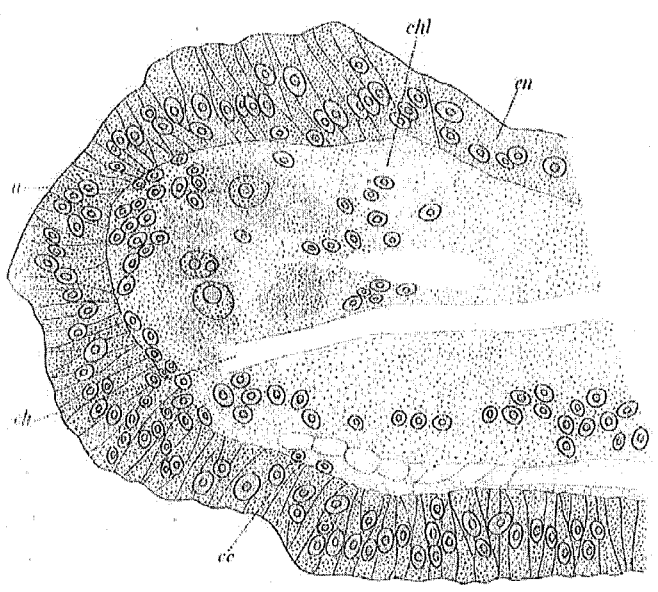
[67] N. KLEINENBERG, *Hydra, eine anatomisch-entwicklungsgeschichtliche Untersuchung*, Leipzig 1872; J. LOEB, *Untersuchungen zur physiologischen Mophologie der Tiere. I. Über Heteromorphose*, Würzburg 1891; H. DRIESCH, *Zur Analysis der Potenzen embryonaler Organzellen*, in «Archiv für Entwickelungsmechanik der Organismen», 2, 1895-96, pp. 169-203; E.E. BICKFORD, *Notes on Regeneration and Heteromorphosis of Tubularian Hydroids*, in «Journal of Morphology», 9, 1894, pp. 417-430; T.H. MORGAN, *Experimental Studies of the Regeneration of Planaria Maculata*, in «Archiv für Entwickelungsmechanik der Organismen», 7, 1898, pp. 364-397.

[68] S.L. SINGER, *Adventures Abroad. North American Women at German-speaking Universities, 1868-1915*, Westport CT - London 2003, p. 121.

[69] H. RANDOLPH, *The Regeneration of the Tail in Lumbriculus*, in «Zoologischer Anzeiger», 362, 1891, pp. 154-156, here pp. 154-155; this definition sounds strikingly similar to the one proposed in B. ALBERTS et al., *Molecular Biology of the Cell*, New York 2008[5], p. 1417: stem cells are «cells that are specialized to provide an indefinite supply of fresh differentiated cells where these are lost, discarded, or needed in greater numbers».

[70] H. RANDOLPH, *The Regeneration of the Tail in Lumbriculus*, in «Journal of Morphology», 7, 1892, pp. 317-344, here p. 334.

Figure 5. *Randolph's neoblasts in a sagittal section of a tail of one day of «Lumbriculus variegatus» Grube*



The great size of the neoblast was seen as an indicator of the rapid regeneration process. *ch.* = neurochord; *chl.* = chlorogogue cell; *ec.* = ectoderm; *en.*: = entoderm; *n.* = neoblast

Source: H. RANDOLPH, *The regeneration*, 1892, pl. XIX, fig. 4.

In the late 1890s Randolph switched to her better-known planaria studies; but these, though remarkably systematic, were not conducted at the cellular level[71].

The alternative terminology reigning in regeneration biology is even more curious, considering that the researchers were often the same ones who dominated the embryological debate, and who clearly intuited the analogy to ontogenetic development. Morgan, for example, concluded that «[t]he planarian is about as plastic as any egg that has been experimented upon» and «the material of the body is almost as plastic as

[71] H. RANDOLPH, *Observations and Experiments on Regeneration in Planarians*, in «Archiv für Entwickelungsmechanik der Organismen», 5, 1897, pp. 352-372.

that of an undivided or dividing egg»[72]. Moreover, because very similar results were obtained by dividing blastomeres or cutting pieces of larvae or severing parts of adult organisms, the boundary between embryonic and adult potency had been experimentally blurred. With Randolph's comparison between self-renewal and budding, the distinction between self-regeneration and (asexual) reproduction likewise dissolved. Not linguistically, however. As we have already seen, although until the 1960s the term 'stem cell' had appeared in Wilson's chapter on germ cells, it was never applied in the contexts of self-renewal. Kleinenberg and Randolph even introduced new terms. The reason may have been that the investigation of regeneration shifted to Driesch's holistic conception of development, rather than in the direction of the Roux-Weismann theory, with which the term was linked. It is therefore curious that most present-day definitions of stem cells, stressing their function in self-repair and referring just to the double capacity of differentiation and self-renewal, derive mainly from these studies on the regeneration of somatic tissues of adult organisms. Concept and terminology proceeded along different paths.

Nevertheless, when regeneration biology was finally incorporated, the understanding and mastery of 'stemming' considerably changed. In parallel with the increasingly divergent results obtained with cell cultures, the meaning of 'stem cell' became more complex and blurred. To be a stem cell, the cell needed external information which told it what to do. Efforts to identify and neatly define a specific (and hopefully controllable and exploitable) entity were hampered by the re-discovery of the genetic plasticity of cells in general. Interestingly, it was precisely these insights that permitted botany to re-enter the scene; and today the influence of phytohormones on the riembryonization of adult plant tissues attracts considerable attention.

9. *The cancer stem cell*

Throughout the late nineteenth and early twentieth centuries, embryology continued to be highly productive, developing far-reaching

[72] T.H. MORGAN, *Regeneration of Planaria* 1898, pp. 394 and 396. For recent developments see A. SÁNCHEZ ALVARADO, *Stem Cells and the Planarian Schmidtea Mediterranea*, in «Comptes rendus de biologie», 330, 2007, 6-7, pp. 498-503.

concepts and experimental tools which stimulated many neighboring fields. Some experiments went further in time, manipulating not only the initial stages of cleavage but also later ones. In 1907, for example, the year of his first advances in the hanging drop technology, Ross G. Harrison also experimentally deformed limb buds to create 'monsters'[73]. Yet it was in the field of cancer research that embryology, natural or artificially induced teratogeny, and stem cell studies most profitably met and promised to reveal the bases of pathological development.

From the late nineteenth century onwards, several cellular theories were proposed to explain the appearance and growth of cancer cells. These debates roughly remember the opposition between the localizing and the holistic theories of the contemporaneous discussions on regeneration biology, embryology[74], and shortly afterwards also cell cultures. In 1875 pathologist Julius Friedrich Cohnheim (1839-1884) argued that cancers were due to a surplus of embryonic cells distributed in the tissues which were dormant and eventually activated in adults[75]. Others, like Hugo Ribbert (1855-1920), opposed this view and saw cancer cells as deviations from normal cell growth caused by a disturbed relationship with their neighbor cells. In particular, Carrel's 'immortal' chicken heart cells furnished strong support for the idea that cells go out of control and become immortal when isolated from their controlling organismic context.

These concepts also dominated the debate on the origin of teratomas – benign but bizarre germ cell tumors containing cartilage, teeth, hair, and other tissues. These tumors had been described in humans at least since 1658, and in 1863 they were given the name of 'teratoma'

[73] R.G. HARRISON, *Experiments on the Development of the Forelimb of Ambystoma, a Self-differentiating Equipotential System*, in «Journal for Experimental Zoology», 25, 1918, pp. 413-461.

[74] J.A. WITKOWSKI, *Experimental Pathology and the Origins of Tissue Culture: Leo Loeb's Contribution*, in «Medical History», 27, 1983, 3, pp. 269-288.

[75] V.A. TRIOLO, *Nineteenth Century Foundations of Cancer Research: Advances in Tumor Pathology, Nomenclature and Theories of Oncogenesis*, in «Cancer Research», 25, 1965, pp. 75-106, here pp. 94-95; E. GRUNDMANN, *Die Vorstellungen von Julius Cohnheim zur Geschwülstentstehung und Metastasierung im Blickwinkel neuer Forschungsergebnisse*, in «Zentralblatt für Allgemeine Pathologie und Pathologische Anatomie», 130, 1985, pp. 323-331.

derived from the Greek word for 'monster tumor'[76]. The relationship with the contemporaneous stem cell debates is complex. Although the supporters of the hypothesis of latent embryonic cells scattered throughout the body used terms like 'stem cell', 'embryonic stem tree', or 'stem source' (*Stammquelle*), they gave these special cells different names. French internist Louis Bard (1857-1930) talked in 1888 about *cellule nodale*, pathologist Max Askanazy (1865-1940) in 1907 about *eiwertige Keime* (egg-like germs), *eiwertige Stammkeime* (egg-like stem-germs), and, referring to their origin from blastomeres, *Blastomzellen* (blastoma cells) possessing a 'prosoplastic potency'. Well informed on the contemporaneous embryological debate, Askanazy tried to combine the localizing and the holistic explanations:

«Therefore, we assume that nearly all real teratomas derive from one almost egg-like germ of about the same fetal age and thus of almost the same formative potency, and that it is due only to the special circumstances which inhibit or stimulate this potency»[77].

However, although latently present in all these years, stem cells explicitly entered the scene through a different and probably completely unexpected door: tests on the damage caused by smoking. In 1952, embryologist Leroy Stevens obtained his first job, funded by a tobacco company, at the Jackson Laboratory in Bar Harbor, Maine. He exposed mice to large amounts of cigarette ingredients and then screened them for any kind of mutation. He found teratomas in some male mice of the then famous 'strain 129'.

Stevens left tobacco research and for the next decades concentrated on these tumors. In order to find what he called the 'cell of origin', he tried to increase the frequency of mice afflicted with the disease. It was not until 1967 that Stevens, creating a hybrid strain out of sterile healthy mice and the 129-mice, and on mating these hybrids, discovered that not a single one of the pure-bred sterile mice showed a teratoma. He therefore concluded that the origin must lie in the primordial germ

[76] M. Cooper, *Regenerative Medicine: Stem Cells and the Science of Monstrosity*, in «Medical Humanities», 30, 2004, pp. 12-22, here p. 15.

[77] M. Askanazy, *Die Teratome nach ihrem Bau, ihrem Verlauf, ihrer Genese und im Vergleich zum experimentellen Teratoid*, in «Verhandlungen der Deutschen Pathologischen Gesellschaft», 11, 1907, pp. 39-82, here p. 72: «Danach nehmen wir an, daß fast alle wahren Teratome aus einem fast eiwertigen Keim von ziemlich gleichem Fötalalter und daher ziemlich gleicher Bildungspotenz hervorgehen und daß es nur die besonderen Umstände sind, die diese Potenz hemmen oder fördern».

cells[78]. By good fortune he obtained another colony, called 'LT', with female mice presenting teratomas. About ten percent of these females, though still virgins, were pregnant. Stevens assumed that these 'embryos' were teratomas due to parthenogenesis, i.e. embryonic growth without fertilization. The connection between teratomas and (disturbed) embryonic growth was not particularly new, as nineteenth-century names like 'parasitic monstrosity' or 'permanent embryo' demonstrate. Yet Stevens furnished the convincing proof and found a way to induce it experimentally. By grafting the inner mass of early embryos into the testes of adult mice, he obtained growths which behaved like teratomas, and noted that:

«Pluripotent embryonic cells appear to give rise to both rapidly differentiating cells and others which, like themselves, remain undifferentiated. It seems clear from these studies that embryonic-type cells which do not undergo adult-type histogenesis are responsible for progressive growth»[79].

Independently, pathologist Gordon Barry Pierce called them 'multipotential cells'[80], and traced the origin of teratocarcinomas, the malignant germ cell tumors, back to a few embryoid bodies. The cells located inside these bodies were later called 'embryonal carcinoma cells' (EC cells) and identified as the multipotent cells of the teratocarcinoma. They could be transplanted to induce tumor growths, or they could be cultured *in vitro*[81]. Stevens then succeeded in generating teratomas and teratocarcinomas from normal germ cells or from early mouse embryo cells by transplanting them into different tissues[82]. In 1970 the first murine teratocarcinoma cells were adapted to *in vitro* culture as permanent embryonic carcinoma cell lines. Teratoma studies were thus connected with the cell culture technology. Yet, even more astoni-

[78] L.C. Stevens, *Origin of Testicular Teratomas from Primordial Germ Cells in Mice*, in «Journal of the National Cancer Institute», 38, 1967, pp. 549-552.

[79] L.C. Stevens - C.C. Little, *Spontaneous Testicular Teratomas in an Imbred Strain of Mice*, in «Proceedings of the National Academy of Science, USA», 40, 1954, 11, pp. 1080-1087, here p. 1080.

[80] G.B. Pierce - F.J. Dixon, *Testicular Teratomas I. The Demonstration of Teratogenesis by Metamorphosis of Multipotential Cells*, in «Cancer», 12, 1959, pp. 573-583.

[81] I. Damjanov, *The Road from Teratocarcinoma to Human Embryonic Stem Cells*, in «Stem Cell Reviews», 1, 2005, pp. 273-276.

[82] L.C. Stevens, *The Development of Transplantable Teratocarcinomas from Intratesticular Grafts of Pre- and Post-implantation Mouse Embryos*, in «Developmental Biology», 21, 1970, pp. 364-382.

shing results followed. Beatrice Mintz and Karl Illmensee, for example, showed in 1975 and 1978 that normal cells could become malignant when removed from their tissues, whereas malignant teratocarcinoma cells could become benign when placed in a 'normal' environment; and Sidney Strickland and Vijak Mahdavi of the Rockefeller University induced nullipotent embryonic carcinoma cells to differentiate only by exposing them to retinoic acid[83].

With cancer research the meaning of stem cells again changed:

1. Cancer researchers, too, used an alternative terminology for many years. Although Askanazy spoke of the *stem* source of teratomas[84], and Stevens declared that «ovarian teratomas *stem* from embryonic undifferentiated cells [my emphasis]»[85], they preferred expressions like 'prosoplastic egg-like germs', 'multipotential embryonic cells', 'pluripotent embryonic cells', and then 'embryonal carcinoma cells'. These researchers were well informed about the Driesch-Roux debate; hence the reasons for this was not ignorance but rather may have been the same as those in regeneration biology.

2. Although 'embryoid bodies' do not represent embryos, and although initially only cancer research was involved[86], the research on teratomas and teratocarcinomas marked the return of the 'embryonic' stem cell. A conceptual link among cancer research, embryology, and stem cells existed at least since Cohnheim's theory of 'embryonic rests'. After the inner cells of mice blastocysts had been grafted, the relationship among the three fields assumed a more concrete meaning. In the following years, an increasing number of stem cell technologies traced their origin to experimental embryology.

3. The investigation of embryonic carcinoma cells blurred the neat distinction between normal (differentiated) and cancerous (undifferentiated) cell division. The possibility of experimentally inducing normal cells to become malignant, and *vice versa* of reverting tumor stem cells

[83] P.W. Andrews, *From Teratocarcinomas to Embryonic Stem Cells*, in «Philosophical Transactions of the Royal Society. Biological Sciences», 357, 2002, 1420, pp. 405-417.

[84] M. Askanazy, *Die Teratome* 1907, p. 71.

[85] L.C. Stevens - C.C. Little, *Spontaneous Testicular Teratomas*, 1954, p. 1086; similar in G.B. Pierce - F.J. Dixon, *Testicular Teratomas*, 1959, p. 573.

[86] M. Cooper, *Immortal Hydra* 2003, p. 18.

to normal behavior, reopened the debate on context dependency, while also giving greater plausibility to the concept of Maximov's micro-environment, as well as to that of Driesch's prospective potency. Besides the practical and ethical implications of using cancerous stem cells[87], this debate also created an ontological and terminological problem: if a cell is only a stem cell when it is surrounded by the right environment, is a stem cell really a distinct entity that merits a proper name?

4. The great potency of proliferation and the multipotency of the embryonic carcinoma cell lines did not only furnish an extraordinary model object for the study of cell division and differentiation; they also created unexpected technical problems, in particular the need to halt the seemingly never-ending intention of these cells to proliferate. Curiously, this reminds us that the (English) word 'stemming' does not only mean 'deriving' but also 'tamping', 'plugging' or 'holding back'.

10. *Conclusions: Stem cell terminology*

On considering the various research fields that during the decades around 1900 were engaged in investigating phenomena that today are ascribed to the activity of stem cells, there emerges a picture rich in questions, approaches, concepts, tools, methodologies, and lines of thought. Although these are linked to different contexts, they have all contributed to, and still to some degree influence, the way in which stem cell researchers work and think today. Nik Brown has been intrigued that «at any particular historical moment, a stem cell is a different thing»[88]. And indeed, as we have seen, the term 'stem cell' denoted, and still denotes, a multitude of overlapping things: 1. an anatomical entity (a cell of a stem); 2. a phylogenetic entity (the very first life form); 3. an ontological entity (the fertilized egg cell); 4. a genetic entity of general development (the germ-line cell); 5. a genetic entity of specific development (regeneration); 6. a special anatomical entity with distinct morphological features; 7. a special anatomical entity recognizable only through its specific function; 8. a temporary

[87] For recent implications see A.M. Wobius, *The Janus Face of Pluripotent Stem Cells – Connection between Pluripotency and Tumourigenicity*, in «Bioessays», 32, 2010, 11, pp. 993-1002.

[88] N. Brown et al., *Promissory Pasts* 2006, here p. 338.

condition of an anatomical entity which, due to its environment, performs a specific function at a specific moment; 9. an entity that lies at the basis of a normal/pathological divide (embryonal carcinoma cells); 10. an entity that raises hopes for easy manipulation and great clinical-therapeutic as well as economic expectations and 11. (an aspect not treated in this paper) an entity that provokes ethical fears. Which of these things represent a real object and which a mere speculative one is still a matter of debate. Interestingly, during the period considered here, those researchers who expressly used the term 'stem cell' did so with a meaning somewhat different from that of today, whereas those who used an alternative terminology often talked about objects which today are identified as stem cells.

The continuous metamorphosis of the meaning of the word 'stem cell' is indeed striking, and it does not seem that it will cease in the near future. However, throughout its 150 years of history the meaning has not changed completely. Still today the term probably exerts its most powerful influence through the stem metaphor introduced by Haeckel. It was well suited to several subsequent stem cell concepts, especially to the ontogenetic and initial hematological ones. The subculturing of *in vitro* cell lines reinforced the meaning of branching from one original shoot. It initially adapted less well to the phenomena of regeneration and cancer growths, where it proved much more difficult to trace the sudden activation back to specific cells. Also the connection between the stem metaphor and Weismann's concept of irreversible differentiation through a progressive restriction of potency – though not made by Weismann himself – represents a linking theme in stem cell history. Today, exactly this aspect is questioned by some, and it is the task for future scholars to judge whether stem-ness is really due to (ancestral) derivation, and whether the understanding of stemming as a linear process is due to the stem metaphor rather than to scientific proofs. In fact, the most skeptical are opposed to the term 'stem cell'. On receiving a proper name, the stem cell obtained its epistemological autonomy, but today as throughout its history, doubts arise as to whether the complex phenomenon of proliferative and regenerative potency of some forms of living matter really relies on discrete and structurally well-defined entities.

The history of the word reflects the history of the research field. Even if one wants to confine the history of stem cell research to the period

during which the term 'stem cell' was used, this history is by no means linear. On the contrary, it underpins the extreme interconnectedness among the different research fields, characterized by a continuous migration of persons, concepts, technologies and terminologies. And it is (still?) not a story of continuous stabilization and increasing concreteness; rather, it resembles a constant weaving and unweaving of many threads, a history of salience and fragmentation. At some moments the supposed ontological counterpart of the term 'stem cell' has become more concrete and even manageable; at other moments it has seemed to vanish again. This ongoing uncertainty is due principally to the circumstance that stem-ness concerns a broad spectrum of expressions which lie at the heart of the phenomenon of life itself.

The doubts about what exactly constitutes a stem cell, however, did not compromise the vitality of stem cell research. Scientists worked rather well with unsettled definitions and changing terminologies as long as a certain degree of common understanding reigned among researchers. Things changed when stem cell research became an issue of broader public, political, and legal debate. Decision-makers and law-givers need to circumscribe their objects of concern as neatly as possible. Also the public image of science as producing reliable knowledge is suffering from what is seen as uncertainty. However, I do not think that this dilemma will find a solution in the near future.

Stem Cells, Reversibility and Reprogramming: Historical Perspectives

by *Christina Brandt**

1. *Reprogramming and ideas of reversibility in recent stem cell and cloning research*

Today, 'reprogramming' is a key concept in the field of stem cell and cloning research. The idea that developmental processes can be explained by comparison with computer programs and cybernetic models had its heyday during the 1970s. But nowadays the metaphors of 'genetic programs' or 'developmental programs' are strikingly absent from the literature. Instead, we find an increasingly amount of literature dealing with issues of 'reprogramming'. With respect to the latter, it is not primarily the historically longstanding comparison of organisms with machines (such as the computer) which is at stake. Rather, the practices of 'reprogramming' are at the center of a new approach in the life sciences which fundamentally affects understanding of the reversibility of organismic processes in time. By metaphorically suggesting that it is possible to 'reset' the internal time of a cell, and by propounding the idea that it might be possible to reverse processes in time by going in some sense 'backwards' in differentiation, the notion of 'reprogramming' is part of new scientific visions of technically controlling life processes. This issue of reversibility seems to be at the very center of what cloning and stem cell research – and the high hopes for its applications in regenerative medicine – is about today.

In a review of that research field, published by Rudolf Jaenisch and Richard Young in the journal «Cell» in 2008, the authors summarize the rapid developments of recent years and provide definitions of such basic terms as «totipotent», «pluripotent», «multipotent», «reprogramming»

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and «transdifferentiation plasticity». Reprogramming is defined as: «Increase in potency, dedifferentiation. Can be induced by nuclear transfer, cell fusion, genetic manipulation»[1]. It is described as a biotechnically induced, or, in specific cases, naturally occurring process that increase potency, although the detailed mechanisms are still unknown. Jaenisch and Young explain: «one of the key issues raised by nuclear cloning relates to the mechanism of reprogramming, i.e., how to define the 'reprogramming factors' in the egg cytoplasm that convert the epigenome of a somatic cell into that of an embryonic cell»[2]. 'Reprogramming' has become synonymous with the idea of a reversal of differentiation (it is explicitly defined as «dedifferentiation»), although the function of reprogramming factors and the molecular pathways of reprogramming are still unclear. Moreover, 'reprogramming' has become a research field in its own right[3]. Jaenisch and Young differentiate four «strategies»[4] in the area of reprogramming somatic cells: on the one hand, they refer to practices such as cell nuclei transfer or cell fusion, which are rooted in embryological transplantation experiments or experiments in cell biology developed since the mid-twentieth century. On the other hand, they describe very recently developed practices of what can be called '*in vitro* reprogramming': attempts to reprogram somatic cells «back to an ES-like state»[5] by using techniques of genetic engineering, namely the introduction of genetic elements into the genome. This was first successfully done by Shinya Yamanaka and Kazutoshi Takahashi, who reprogrammed somatic mouse cells by the viral mediated induction of specific transcription factors such as the so-called Oct4, Sox2, c-myc, and Klf4. Published in 2006, Yamanaka and Takahashi's experiments were immediately regarded as heralding a new revolution in life sciences. These results demonstrated that an adult somatic cell could be turned into a pluripotent embryonic stem cell-like state simply by introducing specific genetic elements. The resulting stem cell-like cells soon came to

[1] R. JAENISCH - R. YOUNG, *Stem Cells, the Molecular Circuitry of Pluripotency and Nuclear Reprogramming*, in «Cell», 132, 2008, pp. 567-582, here p. 568.

[2] *Ibidem*, p. 567.

[3] For example, the journal «Cloning and Stem Cells» was renamed «Cellular Reprogramming» (with Ian Wilmut as editor-in-chief) in 2010.

[4] R. JAENISCH - R. YOUNG, *Stem Cells, the Molecular Circuitry*, p. 571.

[5] *Ibidem*.

be called «induced pluripotent stem cells» (iPS), and this very rapidly became the established terminology[6].

The new research on reprogramming seems to aim at technical skills which would enable scientists to reset the differentiated cell, that is, to reverse differentiation in order to create a stage of a new cellular origin, which is the technical starting point for those applied bioengineering techniques in stem cell and embryo research on which rest all the hopes of future possibilities of tissue renewal in regenerative medicine. This seems to go far beyond older attempts to artificially manipulate an organism or parts of an organism, which had, of course, a long tradition in twentieth-century biology reaching back to the engineering ideal in the period of Jacques Loeb. At a deeper level, this seems to show a changed attitude towards temporal processes. The metaphor of «reprogramming», understood as «dedifferentiation», expresses the belief that techniques of bioengineering could enable the scientist to transcend the natural time of a differentiated cell by, in some sense, reversing cellular time. This seems to be a fundamentally new approach at the turn of the twenty-first century.

However, ideas of reversibility are not completely new in the field of stem cell research, although they seem to have disappeared for a while. Furthermore, also the metaphor of «reprogramming» originated in cloning research on frogs in the late 1960s and early 1970s[7]. In what follows, the focus is restricted to the history of stem cell research since the late 1960s and 1970s. The aim is to furnish historical understanding of shifts in basic concepts such as the notion of an embryonic stem cell itself and related ideas of cellular reversibility. The article traces the history of these concepts in the research that was conducted on mouse embryos and murine cell lines in the 1970s, since this was a period which saw the development of scientific practices that enabled the production of the first embryonic stem cell lines. The first part of the article gives a very brief outline of the existing historiography of stem cell research; the second part deals with the main developments

[6] K. Takahashi - S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, in «Cell» 126, 2006, pp. 663-676.

[7] J. Gurdon, *From Nuclear Transfer to Nuclear Reprogramming. The Reversal of Cell Differentiation*, in «Annual Review of Cell and Developmental Biology», 22, 2006, pp. 1-22.

in mammalian embryology since the 1960s; the third and fourth parts are concerned with the emergence of so-called teratocarcinoma stem cell research and related issues of «reversibility» in the 1970s; the fifth, and last section, discusses the advent of the first (murine) embryonic stem cells in the early 1980s, and it explores shifts that redirected the 1970s debate on stem cells and reversibility.

2. *Histories of stem cells*

Embryonic stem cell research and cloning have raised strong ethical concerns and controversial discussions. During the last decade, numerous articles on ethical and social issues concerning stem cell research were published, often written from a science and public policy perspective[8]. However, historical studies, which would yield better understanding of the trajectories of the very recent scientific developments, are still rare. To date, only a few historical attempts have been made to analyze recent stem cell technologies within a broader scientific and cultural context. In *Whose View of Life. Embryos, Cloning and Stem Cells*, historian of biology Jane Maienschein offers a rich picture in which recent stem cell research is explored as part of a longstanding tradition of embryo research, different (epigenetic or preformationist) views of the developing embryo, and related debates about the essence of life[9]. Melinda Cooper discusses the recent stem cell approaches in regenerative medicine against the historical background of scientific and cultural models of regeneration and self-organization from around 1800 until the early twentieth century[10]. Historical overviews more restricted to the late

[8] Among the huge number of studies see for example: N. SNOW (ed.), *Stem Cell Research. New Frontiers in Science and Ethics*, Notre Dame IN 2003; C. HAUSKELLER (ed.), *Humane Stammzellen – therapeutische Optionen, ökonomische Perspektiven, mediale Vermittlung*, Lengerich 2002; C. HAUSKELLER, *How Traditions of Ethical Reasoning and Institutional Processes Shape Stem Cell Research in the UK*, in «Journal of Medicine and Philosophy», 29, 2004, 5, pp. 509-532; H. GOTTWEIS - B. SALTER - C. WALDBY, *The Global Politics of Human Embryonic Stem Cell Science. Regenerative Medicine in Transformation*, London 2009.

[9] J. MAIENSCHEIN, *Whose View of Life? Embryos, Cloning, and Stem Cells*, Cambridge MA 2003.

[10] M. COOPER, *Rediscovering the Immortal Hydra: Stem Cells and the Question of Epigenesis*, in «Configurations», 11, 2003, pp. 1-26.

twentieth century have been published mainly by the scientists themselves actively engaged in stem cell and cloning research[11]. Here, the focus is on scientific developments in embryology, cell biology, developmental mouse genetics, cancer research and related fields of the past four or five decades. Davor Solter, former director at the Max Planck Institute of Immunobiology in Freiburg, describes human embryonic stem cell research as a late outcome of research on teratocarcinoma cell lines in the 1970s. For Solter, embryonic stem cell research provides historical support for the «old truism that unfettered basic research driven only by scientific curiosity is usually the best way to discover things of enormous practical value»[12]. From this perspective, work in the 1970s on cell lines derived from a very special testicular tumor of mice, the so called «teratoma» or «teratocarcinoma»[13], provided the basis for the origin of the first embryonic stem cells, which were isolated directly from mouse embryos in 1981. Solter stresses the «continuities» in research of the past four decades by discussing «crucial discoveries that transformed the study of teratocarcinoma and embryonic stem cells from an esoteric subject into one that now occupies the centre of attention of the biomedical scientific community»[14]. He argues that research on mouse and human material developed along similar lines, although, in his view, «advances using human cells usually lagged behind a decade or so»[15]. In a similar way, Peter Andrews emphasizes that «many of

[11] In addition to the approaches mentioned below, Melinda Fagan has recently explored the history of research on hematopoietic stem cells in the last decades by focusing on the work of Irving Weissman and his group at Stanford University Medical Center, see M.B. FAGAN, *The Search for the Hematopoietic Stem Cell: Social Interaction and Epistemic Success in Immunology*, in «Studies in History and Philosophy of Biological and Biomedical Sciences», 38, 2007, pp. 217-237; M.B. FAGAN, *Stems and Standards: Social Interaction in the Search for Blood Stem Cells*, in «Journal of the History of Biology», 43, 2010, pp. 67-109.

[12] D. SOLTER, *From Teratocarcinomas to Embryonic Stem Cells and Beyond: A History of Embryonic Stem Cell Research*, in «Nature Reviews Genetics», 7, 2006, pp. 319-327, here p. 326.

[13] This tumor is a rare phenomenon in nature. It occurs spontaneously in testis and – seldom – ovaries and it has a very particular composition, containing such tissues as muscles and skin as well as pieces of teeth, bones, hair, etc. The name refers to the Greek word «teratos» (monster).

[14] D. SOLTER, *From Teratocarcinomas to Embryonic Stem Cells*, p. 319.

[15] *Ibidem*, p. 319.

the ideas that are now discussed have a long history and much has been underpinned by the earlier studies of teratocarcinomas, and their embryonal carcinoma (EC) stem cells ...»[16]. Andrews does not only trace the origins of embryonic stem cell research back to theoretical and experimental developments in the 1970s. In an article published in 2002, he also argues that observations in stem cell plasticity will lead to a rethinking of central concepts in developmental biology, such as «reversion» and «de-differentiation» of cells[17]. Today, as said in the first section, these issues are indeed at the center of the very recent scientific advances in the field of stem cell research and cellular reprogramming.

A different, and at first sight unrelated, history of embryonic stem cell research is provided by Robert Edwards. The Nobel prize-winner and pioneer of IVF research refers to experimentation on preimplantation embryos in reproductive medicine as one of the most important research fields, and in which the first attempts to create mammalian embryonic stem cells were made in the 1970s and early 1980s. In 2001, only a few years after the first human embryonic stem cell lines had been successfully isolated by two research groups in the United States[18], Edwards published a short article in «Nature» on «IVF and the history of stem cells»[19]. Here, as well as in further, more personal, reports[20], he reconstructs the history of (human and murine) embryonic stem cell research as a hidden (albeit often neglected) story behind past medical research on *in vitro* fertilization. On this view, the his-

[16] P.W. ANDREWS, *From Teratocarcinomas to Embryonic Stem Cells*, in «Philosophical Transactions: Biological Sciences», 357, 2002, pp. 405-417, here p. 405.

[17] *Ibidem*, p. 413.

[18] James Thomson at the University of Wisconsin/Madison (J.A. THOMSON et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, in «Science», 282, 1998, pp. 1145-1147) and the group of John Gearhart at the Johns Hopkins University (M.J. SHAMBLOTT et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, in «Proceedings of the National Academy of Sciences», 95, 1998, pp. 13726-13731).

[19] R. EDWARDS, *IVF and the History of Stem Cells. Embryo Stem Cells are Poised to Fulfill Their Considerable Historical Potential*, in «Nature», 413, 2001, pp. 349-351.

[20] R. EDWARDS, *Personal Pathways to Embryonic Stem Cells*, in «Reproductive BioMedicine Online», 4, 2002, 3, pp. 263-278; R.G. EDWARDS, *History of Embryo Stem Cells*, in R. LANZA et al. (eds), *Handbook of Stem Cells*, vol. 1: *Embryonic Stem Cell*, Boston MA 2004, pp. 1-14.

torical origin of embryonic stem cell research goes back to the early 1960s, when scientists working on rabbit and mouse embryos not only improved techniques for culturing embryos *in vitro*, but also tried to develop techniques for isolating cell cultures from parts of the early embryo, especially cells from the inner cell mass of the blastocyst. In particular, Edwards cites his collaborative efforts with Robin Cole and John Paul (Glasgow) to produce cellular outgrowths of the early rabbit embryo *in vitro*[21]. According to Edwards, this approach led to the isolation of the first ever mammalian (rabbit) embryonic stem cells (dated by Edwards at 1963)[22] followed by the isolation of cell cultures of the mouse blastocyst, which was successfully achieved by his PhD student Richard Gardner shortly thereafter[23]. As is described in more detail below, Gardner's work eventually resulted in the creation of the first (so-called) «injection» mouse chimera in 1968.

In Edwards' historical reflection, early research on *in vitro* fertilization with human eggs was a multifaceted project that, from the outset, was aimed at a variety of applications, among them not only diagnostic

[21] R. EDWARDS, *IVF and the History of Stem Cells*, see also R.J. COLE - R.G. EDWARDS - J. PAUL, *Cytodifferentiation in Cell Colonies and Cell Strains Derived from Cleaving Ova and Blastocysts of the Rabbit*, in «Experimental Cell Research», 37, 1965, pp. 501-504; R.J. COLE - R.G. EDWARDS - J. PAUL, *Cytodifferentiation and Embryogenesis in Cell Colonies and Tissue Cultures Derived from Ova and Blastocysts of the Rabbit*, in «Developmental Biology», 13, 1966, pp. 385-407.

[22] See R. EDWARDS, *IVF and the History of Stem Cells*, p. 351; Cole, Edwards and Paul explicitly stated in their 1965 paper: «This is a report of successful attempts to culture tissue from rabbit embryos aged between the fertilised egg and the 6-day blastocyst and to initiate cell strains from the blastocyst» (R.J. COLE - R.G. EDWARDS - J. PAUL, *Cytodifferentiation in Cell Colonies*, p. 501); «The embryonic potentialities of these cells are being actively investigated to determine to what extent they have retained a capacity for further cytodifferentiation, with a view to their possible usefulness in embryological studies» (*ibidem*, p. 504).

[23] With hindsight, Edwards (R.G. EDWARDS, *Personal Pathways*, pp. 267-268; and R.G. EDWARDS, *History of Embryo Stem Cells*, pp. 5-6) regards the work of Richard Gardner as part of a broader research plan that «aimed at the properties of embryo stem cells and their therapeutic uses» (R.G. EDWARDS, *History of Embryo Stem Cells*, p. 5). However, in a review on research on embryonic cell cultures, Michael Sherman summarized in 1975: «Although Gardner (1971) has shown that disaggregated single ICM (i.e. *Inner Cell Mass*, C.B.) cells when injected into a second blastocyst can differentiate along with the host ICM cells, efforts to clone isolated blastocyst cells in culture have as yet been unsuccessful» (M. SHERMAN, *The Culture of Cells Derived from Mouse Blastocysts*, in «Cell», 5, 1975, pp. 343-349, here p. 344).

and therapeutic uses (such as the «diagnosis of genetic disease in embryos»[24] or the treatment of infertility) but also the establishment of *in vitro* models for the study of early mammalian development. Finally, Edwards describes medical research on IVF as a field in which visions of future clinical uses of stem cells for tissue renewal arose very early. On hindsight, the work with preimplantation embryos provided research material not only for attempts to produce and to improve tools for the purposes of reproductive medicine (such as maturing oocytes, techniques to handle oocytes, eggs, and embryos of rabbits, mice, and later on, humans *in vitro*), but also embryological tools for the study of cell differentiation and for attempts to produce human embryonic stem cells. With respect to these last, Edwards today interestingly refers to approaches in his laboratory in Bourne Hall that, presumably due to ethical concerns, were difficult to publish in the early 1980s[25].

Whereas these histories, written by scientists who were themselves engaged in the field of embryo and stem cell research, apparently tend to stress theoretical and practical continuities over the past four or five decades, historian of science Michel Morange reminds us of the «permanent transformation in science of 'objects' and objectives»[26]. Morange also traces recent stem cell research back to the work on teratocarcinoma stem cells in the 1970s. His focus, however, is not on continuities but rather on discontinuities in research objects, theoretical assumptions, and practices. These discontinuities are due to conceptual shifts as well as to shifts in the research goals given at specific times within past decades. Arguing that «human ES cells are not the human equivalent of mouse ES cells if one considers the motivations and goals attendant upon their creation», Morange writes:

«The road from mouse EC cells to human ES cells is far from straight – which explains the long delay needed to go from mouse ES cells to human ES cells. A scientific discovery has no value *per se*. It acquires this value and interest in a particular scientific and general context»[27].

[24] R.G. EDWARDS, *Personal Pathways*, here p. 265.

[25] R.G. EDWARDS, *History of Embryo Stem Cells*, here p. 7.

[26] M. MORANGE, *What History Tells Us VII. Twenty-five Years Ago: The Production of Mouse Embryonic Stem Cells*, in «Journal of Biosciences», 31, 2006, 5, pp. 537-541, here p. 540.

[27] *Ibidem*, p. 540.

Morange points to a fundamental shift from the research on teratocarcinoma stem cells in the 1970s to human embryonic stem cell research after 1998. Whereas the 1970s approaches were elements in a broader field of theories of cancerogenesis, today embryonic stem cell research is mainly part of regenerative medicine. As a research field, stem cell studies have today lost the knowledge on the close relationship between cancer and stem cells. Morange also stresses an important historical insight: that human embryonic stem cells (since 1998) and murine embryonic stem cells (since 1981) are different objects, because of the different scientific conditions and research questions and contexts in which they have taken shape. The historical complexity behind recent embryonic stem cell research is already evident from Morange's brief survey. However, numerous questions have not yet been answered, or have not even been raised: What were the theoretical research problems (and the research traditions behind them) that scientists dealt with in developing stem cell research? What kinds of practical requirements guided the work on embryos and related cell cultures in the 1960s and 1970s? Where were the international research centers and how was this research funded? To understand the very recent scientific developments, one must go back to the diversified research landscape of that time. Agriculture-related research on reproduction, cancer research (which received a large amount of financial support, especially in the 1970s), developmental biology, embryology, cell differentiation studies and somatic cell genetics, as well as early attempts in reproductive medicine, constituted very different research fields in which techniques of cell culturing and manipulating embryos *in vitro* originated in the post-war period. This variety of disciplinary fields and theoretical problems, however, was not accompanied by an equal variety of research models. Rather, a common ground for these different approaches was the mouse embryo. Besides rabbits (which had been standard research objects in reproductive biology since the beginning of the twentieth century) and amphibians (which also had a long tradition as research models in experimental embryology, and which, in the case of the frog *Xenopus*, became the main research model for developing cloning techniques such as somatic cell nuclear transfer (SCNT) from the late 1950s onwards)[28], inbred mice strains, mouse embryos, and, in

[28] J.B. GURDON - N. HOPWOOD, *The Introduction of 'Xenopus laevis' into Developmental Biology: of Empire, Pregnancy Testing and Ribosomal Genes*, in «International Journal of Developmental Biology», 44, 2000, pp. 43-50.

particular, so-called mouse chimeras, became dominant research objects in the 1960s and 1970s. A detailed historical reconstruction of these different research contexts, the shifting motivations and the changing research goals is still lacking, and so too is a detailed analysis of how new methods and techniques were developed in the second half of the twentieth century. Also a historical analysis of social and political aspects is still awaited. Whereas, in recent years, historians of molecular biology and genetics have been able to provide a detailed picture of the institutional landscape and social dynamics of the new, molecular life sciences, the parallel history of leading research institutions, as well as the emerging network of collaborating and competing scientists that drove mammalian embryology and developmental genetics in the 1960s and 1970s, has still to be written. However, only some of these aspects are addressed in what follows. Of especial interest is the emergence of central concepts such as the basic notion of an 'embryonic' stem cell and ideas of reversibility in the research of the 1970s.

Although in the histories briefly outlined above, 1970s work on teratocarcinoma stem cells is often seen as laying the basis for the development of later embryonic stem cell approaches, this is only half of the story. To understand the broader context of the origins as well as the goals of early (murine) embryonic stem cell research, it is necessary to take account of the conjunction of two – previously separate – research lines in the 1970s: on the one hand, attempts to improve techniques of culturing and manipulating embryos *in vitro*, in particular mouse embryos (research rooted in agriculture-related fields as well as in the newly developing mammalian embryology since the 1950s); and, on the other hand, research on cancer, in particular work on murine cell lines derived from a very specific tumor that appears in the gonads of mice: the so-called «teratoma» or «teratocarcinoma»[29]. This research also reached back to the late 1950s and early 1960s, when two scientists, Leroy Stevens (then working at the Jackson Laboratory in Bar Harbour), and Barry Pierce (at the University of Michigan, and, from 1964 onwards, University of Colorado) had started to establish teratocarcinoma cell lines as promising research tools with which to study the causes of tumorigenesis. In the 1970s, a rapidly developing new

[29] Benign tumors of this kind were called «teratomas»; malignant tumors were called «teratocarcinomas».

research field emerged from this conjunction: the widespread use of then so-called teratocarcinoma «stem» cells as promising models for the study of embryogenesis as well as carcinogenesis. These specific cell lines and cell cultures (which turned out to resemble embryonic cells in their biochemical and other properties) were originally derived from mice teratocarcinomas by a specific procedure. Because of their resemblance to – and sometimes even assumed identity with – cells from the early embryo, they were called «embryonal» carcinoma cells (EC cells). As described below, their material properties strongly shaped the concept of an «embryonic» stem cell because they became an implicit reference model for materially identifying those cell cultures that were isolated directly from the developing embryo (and which were named «embryonic stem cells» no earlier than 1981). In what follows, first briefly sketched are the 1960s and 1970s developments in mouse embryology which provided the basis for the 1970s teratocarcinoma stem cell research. Then discussed are the concepts of 'reversibility' which emerged in teratocarcinoma stem cell research in the mid-1970s, and, finally, the shift from work on teratocarcinoma stem cells to those kinds of stem cells directly isolated from mouse embryos.

3. *Techniques of culturing embryos: mouse chimeras in the 1960s and 1970s*

Research on mouse embryos flourished from the late 1950s onwards. In 1958 Anne McLaren (an embryologist then working at the Royal Veterinarian College in London) and John Biggers announced the «successful development and birth of mice»[30] cultivated as early embryos *in vitro*. The scientists had removed embryos in the 8-cell stages from the mouse oviduct, cultivated them in test tubes for a couple of days, and, finally, re-transferred them into a surrogate mother. This foster mouse eventually gave birth to healthy young mice. Using this approach, McLaren and Biggers successfully combined techniques that had been developed in research on cell cultures during the previous decade with veterinarian skills in performing embryo transfers; methods that had been developed in agriculture-related research fields. The results of McLaren and Big-

[30] A. McLaren - J.D. Biggers, *Successful Development and Birth of Mice Cultivated in vitro as Early Embryos*, in «Nature», 182, 1958, pp. 877-878, here p. 877.

gers were regarded as pathbreaking groundwork because they opened up a completely new research horizon: the experimental possibility to manipulate pre-implantation embryos[31]. Around the same time, work with early embryos *in vitro* received further impetus when the veterinarian Ralph Brinster from the School of Veterinary Medicine at the University of Pennsylvania developed a new kind of culture medium that enabled the straightforward growth of mouse embryos in the 2-cell stage up to the blastocyst phase in a plastic Petri dish. This method turned the culturing of early embryos into a laboratory routine[32].

Another fundamentally new outcome of work on mouse embryos were the so-called «mouse chimeras» of the 1960s: artificially created living objects with chimeric genotypes which became widespread research tools in the 1970s and which eventually led to the production of the first transgenic mice in the early 1980s. In 1975, McLaren wrote in a preface to the first textbook on mammalian chimeras:

«This book is on a very specialized topic. The few dozen people in the world who have worked with experimental chimaeras will share my enthusiasm for their beauty, their unexpectedness, the insight that they provide into old questions, and above all for the new questions that they continually raise, questions that one never dreamt existed in the days when an individual had two parents only»[33].

McLaren differentiated between two main uses of chimeras in experimental studies at that time: experimental embryology, in which chimeras were unique tools for tracing the «origin and fate of tissues and cell lineages in development», and developmental genetics, in which chimeras were used as research material to «analyze how genetically different cells collaborate to form an adult animal»[34]. Whereas the former set of questions concerned longstanding embryological problems of cell differentiation, cell lineages and the distribution of cell populations in embryogenesis, the latter also concerned basic research questions in immunology. The first mouse chimeras were produced in the early 1960s. In an article published in «Nature» in 1961, Andrzej Kristof Tarkowski, a young

[31] *Ibidem*; see also V. PAPAIOANNOU, *The Coming of Age of the Transgenic Era*, in «International Journal of Developmental Biology», 42, 1998, pp. 841-846.

[32] A. NAGY - M. GERTSENSTEIN - K. VINTERSTEN - R. BEHRINGER, *Manipulating the Mouse Embryo. A Laboratory Manual*, Cold Spring Harbor NY 2003, pp. 13-15.

[33] A. MCLAREN, *Mammalian Chimaeras*, Cambridge 1976, p. VI.

[34] *Ibidem*, p. 7.

scientist from Warsaw working at the University of North Wales in Bangor at that time[35], described methods with which to aggregate two cleaving mouse embryos, each of them at the 8-cell-stage, in a drop of medium. After transfer into a foster mother, the individual bodies of the resulting mice consisted of cells of both original mouse embryos[36]. Tarkowski's initial approach to fusing embryos was mainly a mechanical procedure. A refined and more gentle experimental way to bring early mouse embryos to fusion was published a few years later, when Beatrice Mintz, another pioneer of twentieth-century mammalian embryology, announced the use of a specific enzyme to break the *zona pellucida* (a kind of membrane around the very early embryo), whose dissolution was the necessary first step to enable the aggregation of two (or even more) disparate embryos[37]. Whereas Tarkowski had called these artificially created objects «chimeras», Mintz used the semantically more neutral term of «allophenic mice», because these organisms showed two different cellular phenotypes at the same time, each attributable to a specific genotype[38]. However, the methods established after Tarkowski's and Mintz's approaches resulted in mosaic mice, which later came to be named «aggregation chimeras». A different technique to produce chimeras (later called «injection chimeras») was explored by Richard Gardner in 1968.

[35] Later, Tarkowski had his own research group in Warsaw. Today, he is regarded as one of the leading scientists in the field of (mammalian) embryology and cloning research of the 1960s and 1970s. Despite the Cold War, he was able to establish research collaborations with West European research laboratories. During the 1960s and 1970s, in particular, he had a long and intensive collaboration with Chris Graham's group at the University of Oxford (see C. GRAHAM, *Andrzej Krzysztof Tarkowski abroad, in Photos and Correspondence*, in «International Journal of Developmental Biology», 52, 2008, pp. 171-178).

[36] A.K. TARKOWSKI, *Mouse Chimaeras Developed from Fused Eggs*, in «Nature», 190, 1961, pp. 857-860.

[37] B. MINTZ, *Experimental Study of the Developing Mammalian Egg: Removal of the Zona Pellucida*, in «Science», 138, 1962, pp. 594-595; M. MINTZ, *Experimentally Genetic Mosaicism in the Mouse*, in G.E.W. WOLSTENHOLME - C.M. O'CONNOR (eds), *Preimplantation Stages of Pregnancy*, London 1965, pp. 194-207; see also A. MCLAREN, *Mammalian Chimaeras*, here p. 12.

[38] B. MINTZ, *Gene Expression in Neoplasia and Differentiation* (Harvey Lectures Series, 71), New York 1978, pp. 193-246, here p. 194.

Inspired by experiments which he had previously performed with Robert Edwards on rabbit embryos[39], Gardner, who at that time was working at the Physiological Laboratory in Cambridge, did not use early embryos in the 2- or 8-cell stages. Instead, he took embryos at later stages; in particular, he worked with blastocysts. He developed a method to obtain cells and cell populations from the so-called inner cell mass (ICM) of the mouse blastocyst. Furthermore, he was able to inject these cells into the blastocoel of another, *in vitro* developing, mouse embryo[40]. Gardner and Edwards had shown that «the blastocyst of the rabbit can develop normally after the removal of a substantial piece of trophoblast tissue»[41]. Moreover, subsequent experiments on mice also demonstrated that «the blastocyst obviously retains some of the remarkable regulative capacity exhibited by cleaving eggs of the mouse», as Gardner put it in 1968[42]. However, the main aim of the work by Edwards and Gardner on rabbits was to gain «control of the sex ratio»[43], i.e. to develop skills for identifying male and female embryos by excising trophectoderm cells[44]. As said, this work may be regarded (with hindsight and following Edwards' view) as a first attempt to produce murine embryonic stem cells. Indeed, Gardner's work made visible the «remarkable regulative capacity»[45] of cells of the blastocyst, although his approach, for the time being, aimed not at the isolation of pluripotent cell lines from the early mouse embryo (an endeavor that remained unsuccessful until 1981), but primarily at the transfer of cells from the blastocyst into other early mouse embryos in order to produce mouse chimeras as tools for embryological research[46].

[39] R.L. GARDNER - R.G. EDWARDS, *Control of the Sex Ratio at Full Term in the Rabbit by Transferring Sexed Blastocysts*, in «Nature», 218, 1968, pp. 346-348.

[40] R.L. GARDNER, *Mouse Chimaeras Obtained by the Injection of Cells into the Blastocyst*, in «Nature», 220, 1968, pp. 596-597.

[41] *Ibidem*, p. 597.

[42] *Ibidem*.

[43] R.L. GARDNER - R.G. EDWARDS, *Control of the Sex Ratio*, p. 346.

[44] R.G. EDWARDS, *History of Embryo Stem Cells*, p. 5.

[45] R.L. GARDNER, *Mouse Chimaeras Obtained*, p. 597.

[46] In his experiments on embryo fusion, Gardner had worked with synchronous embryonic cells (the embryonic cells transferred into the mouse blastocyst had exactly the same «age» (counted in days) as the blastocoel to which they were transferred.

In the 1970s, the model for experimental chimerism was still the mouse. «Since the time when the first viable allophenic mice were produced ... thousands of such individually 'assembled' laboratory artifacts have come into existence», Beatrice Mintz wrote in 1978. «They comprise many different paired combinations of cellular genotypes and have enabled experimental *in vivo* study [*sic*!] of a wide range of questions ... previously inaccessible to investigation»[47]. Although there were attempts to transfer the experimental techniques developed on the mouse embryo to other mammals, only a few chimeric animals resulted: chimeric sheep in 1974, chimeric rabbits and rats in the same year[48].

In 1975, when McLaren declared that only a handful of scientists were working on mouse chimeras, this self-understanding probably arose from earlier experiences. Instead, mouse chimeras became widespread research models in the 1970s, although there were still only a handful of research institutes worldwide acting as centers for scientists wanting to be trained in the skills and methods of mammalian embryology and developmental genetics, which was almost completely done with mouse models. Very prominent among these centers was Philadelphia, since two

As future advances in this kind of research, Gardner mentioned the «transfer of asynchronous cells, of specific types of differentiated cells, and of cells between embryos of different species» (R.L. GARDNER, *Mouse Chimaeras Obtained*, p. 597). The injection of «asynchronous» embryonic cells (embryonic cells that were older, or even cells that had some kind of somatic status) was indeed successfully performed a few years later by Brinster and his team in Philadelphia, see L.A. MOUSTAFA - R.L. BRINSTER, *The Fate of Transplanted Cells in Mouse Blastocysts in vitro*, in «Journal of Experimental Zoology», 181, 1972, pp. 181-192; L.A. MOUSTAFA - R.L. BRINSTER, *Induced Chimaerism by Transplanting Embryonic Cells into Mouse Blastocysts*, in «Journal of Experimental Zoology», 181, 1972, pp. 193-202.

[47] B. MINTZ, *Gene Expression in Neoplasia*, p. 195. Although mice were already standardized research objects in genetics in the mid-twentieth century (see K. RADER, *Making Mice: Standardizing Animals for American Biomedical Research, 1900-1955*, Princeton NJ 2004), the use of mice in embryology was something new at that time. Indeed, it was because of their standardized genetic qualities that mice, «whose inbred strains and known genes make it the species of choice» (B. MINTZ, *Gene Expression in Neoplasia*, p. 194), became main models of mammalian embryology in the second half of the century. See also J.B. ROTHS et al., *Spontaneous and Engineered Mutant Mice as Models for Experimental and Comparative Pathology: History, Comparison, and Developmental Technology*, in «Laboratory Animal Science», 49, 1999, pp 12-34; C. GRAHAM, *Mammalian Development in the UK (1950-1995)*, in «International Journal of Developmental Biology», 44, 2000, pp. 51-55.

[48] A. MCLAREN, *Mammalian Chimaeras*, p. VI.

experts in the field worked at different institutions in that city: Beatrice Mintz, who became one of the leading mammalian embryologists in the US, had assembled a research group at the Fox Chase Cancer Center in the 1960s. Additionally, Ralph Brinster (at the School of Veterinary Medicine of the University of Pennsylvania), was regarded as a pioneer in the field. And also the well-known Wistar Institute of Anatomy and Biology was located in Philadelphia.

Further internationally renowned centers in a rapidly developing, collaborative as well as competitive, network of scientists working on mouse embryos and in the field of mammalian developmental biology were especially located in the United Kingdom: Edinburgh became one of those centers, when McLaren moved to the Unit of Animal Genetics at the University of Edinburgh in 1959, where she formed her own research group. Owing to C.H. Waddington, this institute had already developed a practical goal-oriented research program also aimed at improving farm animal breeding[49]. In 1974, McLaren moved back to London, where she became director at the London Medical Research Council mammalian developmental unit at University College, London[50]. Also working at University College, London, was Martin Evans, who began his research on mouse embryos and teratocarcinoma cell lines at the Anatomy and Embryology Department in the 1970s, and then moved to the University of Cambridge in 1978[51]. Building on a longstanding tradition in physiological reproduction research[52], the University of Cambridge became another important center for research on mouse embryology from the 1960s onwards, and so did Oxford, where, for example, Chris Graham and, later, Richard Gardner worked on mouse embryology[53].

[49] C. GRAHAM, *Mammalian Development, in the UK (1950-1995)*, in «International Journal of Developmental Biology», 44, 2000, pp. 51-55, here p. 51.

[50] J. BIGGERS, *Dame Anne McLaren. Geneticist Resolute in Addressing the Techniques and Ethics of Fertility,* obituary, in «The Guardian», Tuesday 10 July 2007, available on web: http://www.guardian.co.uk/science/2007/jul/10/uk.obituaries

[51] M. GOZLAN, *Sir Martin Evans: Leader of the Stem Cell Revolution Wins Nobel Prize* (Interview), in «Medscape Diabetis & Endocrinology», posted 17 October 2007, available on the web: http://www.medscape.com/viearticle/564324, last accessed 5 January 2012.

[52] See for example C. SCHREIBER, *Natürlich künstliche Befruchtung? Eine Geschichte der In-vitro-Fertilisation von 1878 bis 1950*, Göttingen 2009, here pp. 153-180.

[53] C. GRAHAM, *Mammalian Development.*

«What then appeared as the most spectacular development» in the mid-1970s, as François Jacob, who had recently moved from molecular biology to the developmental biology of the mouse, put it at that time[54], were reports about mouse chimeras being produced by the injection of teratocarcinoma-derived cells into the blastocyst of an *in vitro* developing embryo. In 1974 and 1975 three research groups in the US and the UK worked independently on the production of mouse chimeras by using teratocarcinoma stem cells: Brinster's group in Philadelphia; Mintz (in collaboration with an Austrian postdoctoral fellow, Karl Illmensee; and a collaborative group of scientists from Oxford and London, including Virginia Papaioannou, (then a postdoctoral researcher with a PhD from Cambridge), Richard Gardner (then a lecturer at Oxford) and Martin Evans[55]. The results of some of these experiments were «dramatic and decisive», as Mintz enthusiastically declared at that time: «Normal healthy, genetically mosaic mice were obtained ... In the most successful cases, a single teratocarcinoma stem cell, after injection into a blastocyst, was able to give rise clonally to contributions in the full gamut of somatic tissues»[56].

With these results, not only did research on mouse chimeras become a dynamic on its own which, as described below, finally opened the way to the production of transgenic mouse models, but these experiments were important steps towards isolation of the first embryonic stem cells directly derived from mouse embryos[57], insofar as the theoretical

[54] F. JACOB, *Concluding Remarks*, in L. SILVER - G. MARTIN - S. STRICKLAND (eds), *Teratocarcinoma Stem Cells* (Cold Spring Harbor Conferences on Cell Proliferation, 10), Cold Spring Harbor NY 1983, pp. 683-687, here p. 683.

[55] R. BRINSTER, *The Effect of Cells Transferred into the Mouse Blastocyst on Subsequent Development*, in «The Journal of Experimental Medicine», 140, 1974, pp. 1049-1055; B. MINTZ - K. ILLMENSEE, *Normal Genetically Mosaic Mice Produced from Malignant Teratocarcinoma Cells*, in «Proceedings of the National Academy of Sciences», 72, 1975, pp. 3585-3589; V.E. PAPAIOANNOU - M.W. MCBURNEY - R.L. GARDNER - M.J. EVANS, *Fate of Teratocarcinoma Cells Injected into Early Mouse Embryos*, in «Nature», 258, 1975, pp. 70-73.

[56] B. MINTZ, *Gene Expression in Neoplasia*, p. 225.

[57] M.J. EVANS - M.H. KAUFMAN, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, in «Nature», 292, 1981, pp. 154-156; G.R. MARTIN, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, in «Proceedings of the National Academy of Sciences», 78, 1981, pp. 7634-7638.

context in which these experiments were embedded also provided the frame for the occurrence of murine embryonic stem cells. For the time being, these experiments furnished answers to crucial questions that had arisen within research on teratocarcinomas in the past: whether teratocarcinoma stem cells could be compared with cells in the early embryo, and, in parallel, whether or not teratocarcincoma stem cells could be used as a research model to study «mammalian embryogenesis without embryos»[58]. These practical issues concerning the right tools with which to conduct mammalian embryology were also accompanied by theoretical considerations regarding tumorigenesis, because the driving research questions were part of a broader debate on how to understand the origin of cancer. This discussion had arisen in research on this very specific mouse tumor since the late 1960s.

4. *From teratocarcinoma stem cells to the first embryonic stem cells: concepts of «stem cells», «reversibility» and «dedifferentiation» in the 1970s*

It has often been emphasized that research on teratocarcinomas in mice started as an almost esoteric research field through the efforts of only two scientists in the 1950s: Leroy Stevens and Barry Pierce. Working at the Jackson Laboratory in Bar Harbour, Maine, which was the leading center for mouse genetics at that time, Stevens provided the first description of the occurrence of teratomas in a specific inbred strain of mice (the inbred mouse strain 129) in 1954[59]. In subsequent years, he showed that tumors could be experimentally generated in mice by injecting cell material from teratomas. Comparable to naturally occurring teratomas, the induced ones also consisted of a chaotic array of cell tissues coming from all three germ layers: a monstrous mixture of, for example, neural tissue, muscle tissue, and bone marrow. Furthermore, Stevens was able to observe, after several transplant generations, that «thousands of small structures resembling 5- or 6-day mouse embryos float freely in the ascites fluid» [i.e. a fluid in the abdominal cavity of

[58] G.R. Martin, *Teratocarcinomas and Mammalian Embryogenesis*, in «Science», 209, 1980, pp. 768-776, here p. 769.

[59] L.C. Stevens - C.C. Little, *Spontaneous Testicular Teratomas in an Inbred Strain of Mice*, in «Proceedings of the National Academy of Sciences», 40, 1954, pp. 1080-1087.

mice, C.B.][60]. It was supposed that these structures (which were soon named «embryoid bodies») consisted of cells that «remain undetermined for years, while still retaining their multipotentiality»[61]. Since it was assumed that these cells were similar to cells in the early embryo, the isolated cell lines were called «embryonal carcinoma cells» (EC). This assumption gained further support when it could be demonstrated that – vice versa – the implantation of 5- to 6-day-old mouse embryos (that is, at the blastocyst stage of development) into atypical sites of an adult mouse (i.e. not the uterus but, for example, the abdomen) led to the growth of teratocarcinomas[62].

The embryonal carcinoma (EC) cells very soon became important objects for re-emergence of the so-called «stem cell theory of cancer», a theory of tumorigenesis that had its historical origins in around 1900, and that, after a period of disappearance, had been controversially rediscussed since the late 1960s. In an article of 1964, Barry Pierce and his student Lewis Kleinsmith reported that, after injection into mice, a single embryonal carcinoma cell could develop into a variety of somatic tissues as well as into embryoid bodies. Owing to the capacity of EC cells to develop into different adult tissues (which were representative of the tissue mixture in teratomas), Pierce and Kleinsmith claimed that the «multipotentiality» of embryonal carcinoma (EC) cells had been demonstrated, where by «multipotentiality» was meant a state of undifferentiatedness. Moreover, their results also revealed that «all embryonal carcinoma cells are not alike, but that they vary in their capacity for differentiation, growth, and production of embryoid bodies»[63]. The demonstration of the heterogeneity of tumor cells could not be explained by the view that tumors are caused by somatic mutations

[60] L.C. STEVENS, *The Origin and Development of Testicular, Ovarian, and Embryo-derived Teratomas*, in L. SILVER - G. MARTIN - S. STRICKLAND (eds), *Teratocarcinoma Stem Cells*, p. 33.

[61] *Ibidem*, p. 33.

[62] L.C. STEVENS, *The Development of Transplantable Teratocarcinomas from Intratesticular Grafts of pre- and postimplantation Mouse Embryos*, in «Developmental Biology», 21, 1970, pp. 364-382; D. SOLTER - N. SKREB - I. DAMJANOV, *Extrauterine Growth of Mouse Egg-cylinders Results in Malignant Teratoma*, in «Nature», 227, 1970, pp. 503-504.

[63] L.J. KLEINSMITH - G.B. PIERCE, *Multipotentiality of Single Embryonal Carcinoma Cells*, in «Cancer Research», 24, 1964, pp. 1544-1551, here p. 1547.

in specific cells or changes in the material apparatus of the cell such as chromosomes or genes, because in the latter cases, these changes then should occur in all tumor cells alike. Hence, Pierce and Kleinsmith understood the occurrence of tumor cells not as a result of a somatic cell mutation, but as a result of the uncontrolled development of more less undifferentiated embryonic cells. In sum, they interpreted the demonstrated multipotentiality of a single EC cell not only as providing strong support for the stem cell character of embryonic carcinoma cells (as already suggested by Stevens and others) but also as raising a severe challenge against the «dogma regarding the irreversibility of the malignant change»[64], a dogma that stated, as Pierce put it, «once a cancer cell always a cancer cell»[65]. For Pierce and Kleinsmith, the «results show conclusively that embryonal carcinoma cells have the capacity to differentiate into somatic, adult-appearing tissues; since these tissue have been shown to be benign, it is obvious that the malignant stem cells are constantly differentiating spontaneously into benign, normal-appearing cells, a phaenomenon difficult to reconcile with a somatic mutation or an irreversible type of change»[66]. In subsequent years, Pierce developed an elaborate approach which put forward the idea of a cancer cell as a «caricature» of a normal stem cell and normal processes of tissue renewals. In 1975 he stated:

«It has been a dogma, although a disliked one, that malignant cells arise from differentiated cells by a process of dedifferentiation. Stevens showed that a tumor, albeit a funny little tumor, arose from the stem cells of the species ... This probably means that normal stem cells have alternative pathways of differentiation open to them, one recognizable as a malignant pathway»[67].

These views then became much debated in the late 1960s and, in particular, the 1970s. From a historical point of view, three aspects are important in order to understand this discussion: first, the historical roots of the stem cell theory of cancer, which originated in around 1900 when pathologists began to describe malignant tumors as resulting from

[64] *Ibidem*, p. 1548.

[65] G.B. PIERCE, *Teratocarcinoma: Introduction and Perspectives*, in M. SHERMAN - D. SOLTER (eds), *Teratomas and Differentiation*, London, 1975, pp. 3-12, here p. 3.

[66] L.J. KLEINSMITH - G.B. PIERCE, *Multipotentiality of Single Embryonal Carcinoma Cells*, p. 1548.

[67] G.B. PIERCE, *Teratocarcinoma*, p. 9.

the uncontrolled growth of 'embryonic germs'; second, the notion of a «stem cell» in the late 1960s and during the 1970s; and third, various attempts to explain the origin of teratomas, or tumors and cancer more generally, in the 1970s.

That tumors may originate from embryonic cells that remain, as kinds of residuals, in adult tissues, was an idea formulated already in the late nineteenth century, in particular in the German-speaking landscape of pathology. As Holger Maehle has recently analyzed, the Breslau professor of pathology Julius Cohnheim was the first (in 1877) to state that tumors arise from displaced embryonic cells in the adult body[68]. Cohnheim's views were demarcated from contemporary bacteriological, mechanical and chemical theories on the origin of cancer. Theories on the close relationship of cancer cells with embryonic cells or so-called 'embryonic germs', as well as variations of the «blastomere-theory» of cancer, were further developed by scientists and pathologists in around 1900 (for example, Max Askanazy in Geneva, Felix Marchant in Marburg or Robert Bonnet in Greifswald). In the 1920s, critics increasingly challenged these views until the idea of a malignant displacement of embryonic cells in the adult body was cast in doubt by to the influential work of Emil Witschi (at the State University of Iowa) in the late 1940s[69].

In the 1960s and 1970s, some scientists were well aware of the historical roots of the stem cell hypothesis on cancer. Pierce and Kleinsmith not only explicitly referred to the work of Askanazy but they also adopted a similar view when they explained the origin of teratomas as a «morphogenesis from undifferentiated malignant stem cells»[70]. Also Gail Martin, a postdoctoral fellow working in the group of Martin Evans at the University College, London, at that time (a few years later, independently from the British group, she isolated one of the first murine embryonic cell lines) wrote in one of the first surveys of the field in 1975: «This idea ... is perhaps not as iconoclastic as it may seem: at the end of the 19th century, Cohnheim and Ribbert argued that tumors

[68] A.-H. Maehle, *Ambiguous Cells: The Emergence oft the Stem Cell Concept in the 19th and 20th Centuries*, in «Notes & Records of the Royal Society», 65, 2011, pp. 359-378.

[69] *Ibidem.*

[70] L.J. Kleinsmith - G.B. Pierce, *Multipotentiality of Single Embryonal, Carcinoma Cells*, p. 1544.

arose from embryonic cells released from the normal restraints imposed by surrounding tissues»[71]. And Beatrice Mintz, who was one of the leading scientists in the field, was a former student of Emil Witschi[72]; she too, therefore, was presumably aware of older theories.

When scientists spoke of the «stem cell hypothesis» on cancer in the 1970s, they referred to the idea that tumors are caused by a pathological growth of normal stem cells (not by a genetic mutation or a disorder in gene expression and gene regulation.) But what did it mean to speak of a stem cell in the 1970s?

Although the term «embryonic stem cell» did not exist at that time, the term «stem cell» was widely used. It implied the notion of pluri- or multipotency, and referred, in general, to different systems of adult stem cells. In regard to the meaning of «stem cells» at that time, one should be careful not to equate current understandings of the multiple meanings and often popular connotations of «stem cells» as kinds of beneficial «all-rounders» with former meanings of the term, although the idea of pluripotency was, of course, already important in the twentieth century. The notion of a «stem cell», originally coined by Ernst Haeckel in the late nineteenth century, had been used with a variety of meanings in different fields of biology and pathology since the end of the nineteenth century[73]. The meaning of the original term was substantially underpinned by a genealogical concept because of the evolutionary and embryological context of its first use at the end of the nineteenth century. Because stem cells were viewed as progenitors in a broad sense, the concept of a stem cell was a genealogical one that emphasized the origins or past traces of cells. However, in the course of the twentieth century this genealogical focus shifted towards a concept of stem cell (as it was used in cell biology, pathology, and, later, in medicine) that did not refer primarily to the (evolutionary or embryonic) past traces of cells but to their future possibilities, since the pluripotent status of these cells with respect to the function of tissue-renewal became the

[71] G.R. MARTIN, *Teratocarcinomas as a Model System for the Study of Embryogenesis and Neoplasia*, in «Cell», 5, 1975, pp. 229-243, here pp. 240-241.

[72] In the acknowledgments to her Harvey Lecture, delivered in New York in April 1976, Mintz explicitly stresses the «lasting influence of my former teacher, the late Professor Emil Witschi»; B. MINTZ, *Gene Expression in Neoplasia*, p. 243.

[73] See Dröscher in this volume; A.-H. MAEHLE, *Ambiguous Cells*.

dominant aspect. «Such normal stem cells exist», Jacob wrote in 1983, «not only in the developing embryo, but also in the many tissues that are constantly renewed during adult life – for instance, those cells of the marrow which give rise to the various cellular components of the blood, or cells in the basal layer of the skin that divide slowly and differentiate to renew the skin epithelium»[74]. However, until 1981, when Gail Martin introduced the term «embryonic stem cells»[75], it was (contrary to Jacobs' quotation from 1983) *not* common to call cells of the early embryo «stem cells». At least in the literature on mouse embryology and teratocarcinoma research, one can find more general phrases. Scientists spoke of «embryo cells» in general, of 'primordial germ cells' or of «embryonic cell lines» (in contrast to «embryonal cells», which referred to the cells of the embryoid bodies produced by teratocarcinoma cell lines). This was not only a question of conventions of language use. This aspect also points to an important research problem at that time. The term «stem cell» was defined in cell biology with respect to adult cell populations capable of tissue renewal, which implied the notion of an equilibrium within a stem cell system able both to proliferate into other stem cells and to differentiate into specialized cells. At a symposium of the British Society for Cell Biology in 1977 devoted to stem cells in general, Virginia Papaioannou, J. Rossant and Richard Gardner discussed at length the question as to whether or not one could apply the term «stem cell» to cells from the early embryo:

«It seems clear ... that the concept of a stem cell can only be strictly applied to the adult where renewing cell populations are in equilibrium, such that the number of stem cells remains more or less constant. This means that on average half the progeny of stem cell divisions form new stem cells while half form differentiating cells ...

[74] F. JACOB, *Concluding Remarks*, p. 685.

[75] Martin is usually regarded as having introduced the term «embryonic stem cells» in 1981 (G.R. MARTIN, *Isolation of a Pluripotent Cell*, p. 7635). Before, scientists in general did not call cells in the early embryo «embryonic stem cells». However, in the late 1970s the question was discussed of whether the concept of stem cells could be applied to cells in the embryo, and in this context I have found the term in a text by Virginia Papaioannou from 1979: «As EC stem cells differentiate either within a tumour or in culture, there is evidence that they irreversibly lose their stem cell characteristics, a feature shared with other stem cells, notable embryonic stem cells»; V.E. PAPAIOANNOU, *Interactions between mouse embryos and teratocarcinomas*, in N. LE DOUARIN (ed.), *Cell Lineage, Stem Cells and Cell Determination* (Inserm symposium, 10), Amsterdam 1979, pp. 141-155, here p. 143.

The concept of stem cell populations cannot be readily applied to the early embryo, because it is a developing system rather than one in equilibrium. Embryonic development involves continuous growth with cytological and morphological changes and consequently permanently self-renewing cell populations do not appear until later. In the past the fertilised ovum has often been referred to as a stem cell (e.g. Lamerton, 1976) because it eventually gives rise to all the stem cell populations of the adult body as well as all differentiated tissues. However, the fertilised ovum certainly cannot be considered a classical stem cell. Its function is not to divide and renew itself but to divide and differentiate ... The idea that the fertilised egg is a stem cell has probably arisen because of confusion between the concept of a totipotent cell and a stem cell»[76].

The quotation shows that a narrow concept of «stem cell» – as it was used in cell biology – had become the dominant concept in the second half of the twentieth century, whereas the genealogical concept (as it had been developed in late nineteenth century embryology), as well as the use of the term «stem cell» in the context of embryological studies, had paled in comparison to the first concept. Furthermore, the question of whether or not the term «stem cell» was applicable to embryo cells was part of an ongoing discussion on whether, in mammalian embryogenesis, totipotent cells could be found after the blastomere stage (that is, after the 8-celled embryo). As Papaioannou and her colleagues wrote, the question was: «Is there a population of totipotent cells in early development and are they stem cells?»[77]. The comparison of EC cells with embryo cells within this broader context raised two interrelated questions: «Assuming the totipotency of these stem cells [i.e. embryonal carcinoma cells, C.B.], what is their relationship to normal embryonic cells and what can they tell us about the existence of totipotent stem cells in the embryo?»[78].

The first question, namely the exact relationship between EC cells and embryo cells, raises the problem of tracing the cell lineages of EC cells in order to understand the specific embryonic origin of EC cells (which ultrastructurally were regarded as «remarkably similar»[79] to primordial germ cells and to embryonic ectoderm cells). The second question

[76] V.E. PAPAIOANNOU - J. ROSSANT - R. GARDNER, *Stem Cells in Early Mammalian Development*, in B.I. LORD - C.S. POTTEN - R.J. COLE (eds), *Stem Cells and Tissue Homeostasis*, Cambridge 1978, pp. 49-69, here pp. 49 f.

[77] *Ibidem*, p. 51.

[78] *Ibidem*, p. 61.

[79] *Ibidem.*

(«what can EC cells tell about the existence of totipotent cells in the embryo») touched on general embryological problems concerning how to understand the different stages of the developing embryo with respect to the transformation and differentiation of the potency of different cell populations within the developing embryo. Here, EC cells became a reference point to find «candidates for a stem cell population»[80] in post-blastomere stages of the developing embryo. Whereas the first question was apparently relevant for those scientists who came from the field of cancer research, it seemed to be the second question that made research on EC cells attractive to those scientists who came from the embryological research tradition.

However, a final aspect of the manifold meaning of 'stem cells' in the 1970s should be briefly discussed: the intermingling of the pathological connotations and meanings of normal cell differentiation in the stem cell concept. In the late 1970s, the term 'embryonal carcinoma (EC) cell' became increasingly synonymous with the notion of a 'teratocarcinoma stem cell'. This points up the ambivalent status of these cells and, therefore of the concept of a 'stem cell', at that time. In 1975, when the first symposium on teratomas gathered scientists from such different fields as molecular biology, embryology, oncology, and cell differentiation studies, teratocarcinoma cell lines were seen as promising and fashionable interdisciplinary «model systems for the study of differentiation in oncology and embryology», as the editors of the conference volume, Michael Sherman (from the Roche Institute of Molecular Biology) and Davor Solter (from the Wistar Institute in Philadelphia) emphasized[81]. Teratocarcinoma stem cells had an ambivalent status between pathology and normal cell differentiation. On the one hand, as Mintz critically summarized at the symposium[82], they became a dominant research model for studying normal cell differentiation in embryogenesis without embryos, since it was a «widespread assumption that readily available

[80] *Ibidem*, p. 53.

[81] M.I. SHERMAN - D. SOLTER (eds), *Teratomas and Differentiation*, London 1975, p. XV.

[82] B. MINTZ - K. ILLMENSEE - J.D. GEARHART, *Developmental and Experimental Potentialities of Mouse Teratocarcinoma Cells from Embryoid Body Cores*, in M.I. SHERMAN - D. SOLTER (eds), *Teratomas and Differentiation*, New York 1975, pp. 59-82, here p. 75 f.; Mintz's criticism was that EC cells could not be compared to (totipotent) blastomeres – as was widely assumed – but should be compared to embryo cells at later stages (embryos between 5 to 7 days old), p. 78.

teratocarcinoma cells would ... conveniently provide» the scientists «with a 'barrel' of cells equivalent to the less readily available blastomeres». On the other hand, they were the main objects and actors in a discussion on tumorigenesis in which, as will now be briefly outlined, the notion of reversibility was critically considered.

5. *Teratocarcinoma stem cells and issues of «reversibility» in the 1970s*

A variety of different theories on cancer existed during the 1960s and 1970s. Two main scientific camps can be distinguished as adhering to the genetic versus epigenetic approaches: those who adopted the former saw the origin of tumors inside the cell (or in intracellular molecular interactions), and those who adopted the latter referred to the interaction of the cell and its immediate cellular environment, and hence to the cell-cell interaction.

The idea that cancer originated from somatic mutation became increasingly widespread in the 1970s. On this view, cancer was caused by a kind of genetic error *inside* the cell. Those approaches that located the origin for cancerogenesis primarily at the level of DNA turned into the so-called «oncogene paradigm» – a bundle of theories which explained cancer as being caused by structural modifications of specific genes and which became the dominant explanation for cancer in the 1980s[83]. Nevertheless, still dominant approaches in the 1970s described cancer as primarily a dysregulation of cellular activities, in particular as a deregulation of gene expression[84]. For scientists working with teratocarcinoma cell lines, tumors had to be seen «essentially [as] a disease of dearrangement of cell differentiation and not merely of cell multiplication»[85]. Against this background of debates on the mutational

[83] See M. MORANGE, *From the Regulatory Vision of Cancer to the Oncogene Paradigm, 1975-1985*, in «Journal of the History of Biology», 30, 1997, pp. 1-29; on the history of the oncogene paradigm see also T. VAN HELVOORT, *A Century of Research into the Cause of Cancer: Is the New Oncogene Paradigm Revolutionary?*, in «History and Philosophy of the Life Sciences», 21, 1999, pp. 293-330; J.-P.GAUDILLIÈRE, *Essay Review: Cancer and Science: The Hundred Years War*, «Journal of the History of Biology», 31, 1998, pp. 279-288.

[84] M. MORANGE, *From the Regulatory Vision.*

[85] B. MINTZ, *Gene Expression in Neoplasia*, p. 212.

or non-mutational origin of cancer cells, the close similarities between EC cells and cells from the early embryo became one of the most important features. In 1983, Jacob summarized the matter as follows: «All the work done in the past 20 years or so supports the idea that by all their properties ... EC cells closely resemble multipotential cells of the early embryo». He added:

«The main question, however, is: How close is this similarity? Is there a *necessary* difference, a mutation that is always the same and until now has passed unnoticed by lack of technical means? Or, in contrast, is there no difference at all and is an EC cell exactly the same thing as a multipotential early embryonic cell that has merely been disturbed from its normal geometrical arrangement?»[86].

However, there was not only controversy between the genetic and the epigenetic camps; there were sometimes even more controversial cleavages among the (different) approaches that explained cancerogenesis as a dysregulation of processes of differentiation. In 1978, Mintz stressed that the hypothesis of cancer as a «developmental disturbance» should be seen as a «broad umbrella», under which

«are sheltered such partially diverse views of the ontogenic fault as: dedifferentiation, or loss of differentiated functions in specialized cells (Pitot, 1968); impairment of forward differentiation of stem cells (Pierce, 1974); misprogramming of gene function at any step in differentiation, from the least to the most differentiated cells, resulting in new patterns of gene expression (Markert, 1968); and selective reactivation of some genes involved in early development (Coggin and Anderson, 1973)»[87].

The stem cell theory of cancer as propounded by scientists like Pierce argued not only against a genetic model of cancerogenesis but also against the idea of cancer as a process of «de-differentiation» with the underpinning assumption that tumor cells are transformed cells. To regard a cancer cell as resulting from a process of dedifferentiation implied the idea that the malignant conversion of the cell occurred in terminally differentiated cells because of a loss of specialized functions. The stem cell hypothesis, on the contrary, argued that tumor cells were not transformed cells (which therefore, owing to the process of de-differentiation, would become similar to early embryo cells); rather, tumor cells were 'like' normal stem cells or normal cells from the early embryo. Before Stevens and Pierce published their results, it was a

[86] F. JACOB, *Concluding Remarks*, p. 685.

[87] B. MINTZ, *Gene Expression in Neoplasia*, p. 216.

common belief in pathology that cancer cells could 'not' go through the process of differentiation any more. When Pierce suggested that the teratocarcinoma stem cell could be regarded as a «normal stem cell» which still retained its pluripotency, he implicitly suggested the provocative idea that a tumor cell was still able to differentiate. With this he challenged the «dogma of irreversibility»:

«Roy and I showed that the normal primordial germ cell is no more and no less differentiated than the embryonal carcinoma cells to which it gives origin. There is an overproduction of undifferentiated malignant cells in the tumor. This is not the result of dedifferentiation; rather it is merely the overproduction of undifferentiated cells that have a limited potential for differentiation. This is the caricature. What goes on in tumors is the antithesis of dedifferentiation»[88].

At the core of the dispute between, on the one hand, those scientists who favored the idea of «dedifferentiation» and those, on the other, who favored the view of carcinoma cells as «normal stem cells» was the notion of reversibility, which was discussed on two different levels: On the one hand, with respect to the idea of de-differentiation, the carcinoma cell itself was seen as a «reversibly transformed embryonic cell» (Martin 1980: 775). Here, the notion of reversibility referred «to the idea that neoplastic conversion occurs in terminally differentiated cells and that the fetal gene products observed in tumors are produced as a consequence of dedifferentiation»[89]. On this view, the appearance of embryonic-like cells in tumors was seen as a secondary, derived status – as the result of a transformation of the cell in which the differentiated status of the cell became reversed. Hence, aspects of reversibility were *not* primarily discussed with respect to the status of malignancy but with respect to the secondary transformed character of the cancer cell itself, which had reverted from a specialized or differentiated cell to an embryo-like cell.

However, with the stem cell hypothesis on cancer, the idea of reversibility concerned the view that the malignant status of the cells could be reversed. This view, of course, had an enormous impact on ideas concerning therapeutic applications, and it gave strong support for hopes

[88] J. ARÉCHAGA, *On the Boundary between Development and Neoplasia. An Interview With Professor G. Barry Pierce*, in «International Journal of Developmental Biology», 37, 1993, pp. 5-16, here p. 11.

[89] G.R. MARTIN, *Teratocarcinomas and Mammalian Embryogenesis*, p. 775.

that cancer could be treated in the future[90]. The stem cell hypothesis on cancer was based on the idea that embryonal carcinoma cells, and perhaps also tumor cells in general, «are cells that express a normal embryonic program of continued proliferation until stimulated to differentiate»[91]. In the mid-1970s, this view that embryonic carcinoma cells (EC) were basically normal «embryo cells»[92] (and not reversed differentiated cells) received increasing evidence from morphological, biochemical and serological studies that demonstrated a close similarity between EC cells and cells from early mouse embryos[93].

The common understanding was now that the absence of appropriate signals from the cellular environment was responsible for the malignant pathway of these cells. 'Malignant pathways' meant in this case that the cells continued to proliferate (instead of undergoing the process of cell differentiation). This view also included the idea that the malignant character could be reversed by exposing EC cells to an appropriate cellular environment, such as an embryonic environment which would then be able to stimulate a process of differentiation. In 1975, Martin summarized the different positions assumed at that time, and suggested two different approaches to proving the extent to which a similarity, or even identity, between embryonal carcinoma cells and embryo cells could be confirmed:

«If it were true that embryonal carcinoma cells are normal pluripotent embryo cells, and if it were possible to obtain pluripotent embryo cells by culturing early embryos in vitro, then such cultures should have the same in vitro characteristics as embryonal carcinoma cell cultures, and should form teratocarcinomas when injected into mice ... Perhaps the most critical test of the idea that embryonal carcinoma cells are normal embryo cells would be to determine whether or not, given the 'correct' environment,

[90] Already in 1964, Kleinsmith and Pierce had written: «If cancer cells are not irreversibly changed and do spontaneously undergo differentiation, which in some instances results in benign cells, it would seem appropriate that cancer therapy, rather than attempting to kill or extirpate all the cells of a tumor, might attempt to direct the spontaneously occurring differentiation toward the production of benign tissues as we have postulated previously»; L.J. KLEINSMITH - G.B. PIERCE, *Multipotentiality of Single Embryonal Carcinoma Cells*, p. 1548.

[91] G.R. MARTIN, *Teratocarcinomas and Mammalian Embryogenesis*, p. 775.

[92] G.R. MARTIN, *Teratocarcinomas as a Model System*, p. 241.

[93] F. JACOB, *Mouse Teratocarcinoma and Mouse Embryo. The Leeuwenhoek Lecture, 1977*, in «Proceedings Royal Society London», B 201, 1978, pp. 249-270, here p. 253.

they can form a normal fertile animal. The most appropriate environment to place them in would probably be the inner cell mass (ICM) of a day 4 blastocyst»[94].

It is clear from this quotation that two future research directions would thereafter become important: first, the direct isolation of cells from the early mouse embryo in order to compare the capability of these cells with EC cells; second, the injection of EC cells into a mouse blastocyst in order to produce mouse chimeras as a test for the 'normal' capacities of EC cells. Indeed, the former research direction led to the production of the first murine embryonic stem cells lines in around 1981 – as described in detail in the last section. When Martin wrote her review, scientists were already actively heading in the second research direction. As said, in 1974 Ralph Brinster investigated what kind of effects were exerted by differently aged, non-embryonic cells transferred into a mouse blastocyst on the subsequent development of this mouse embryo, using the method to produce chimeras initially developed by Richard Gardner. Brinster transferred not only asynchronous cells[95] but also teratocarcinoma ones. His research indicated that the transferred cells were partly integrated into the normal development of tissue, prompting him to conclude that «the embryo environment can bring under control the autonomous proliferation of the teratocarcinoma cells»[96]. Shortly afterwards, in September 1975, Mintz and Illmensee reported their sensational finding that the injection of teratocarcinoma cells into mouse blastocysts resulted in healthy mouse chimeras; a finding which was interpreted as providing strong support for the reversibility of the malignant character of EC cells and the identity of EC cells with embryonic cells. «The original conversion to malignancy» of EC cells, Mintz and Illmensee summarized, «has proved to be completely reversible to normalcy»[97]. Other scientists described the situation as a process of redirecting EC cells so that they «differentiate in an ordered way» under the influence of normal embryonic cells[98]. Also the «normalizing» of EC cells was an expression often used in the following years. In

[94] G.R. Martin, *Teratocarcinomas as a Model System*, p. 241.

[95] L.A. Moustafa - R.L. Brinster, *The Fate of Transplanted Cells*; L.A. Moustafa - R.L. Brinster, *Induced Chimaerism*.

[96] R.L. Brinster, *The Effect of Cells Transferred*, p. 1054.

[97] B. Mintz - K. Illmensee, *Normal Genetically Mosaic Mice*, p. 3585.

[98] F. Jacob, *Mouse Teratocarcinoma*, p. 253.

November 1975, only two months after Mintz and Illmensee's report, a third article on the production of teratocarcinoma injected mouse chimeras was published by a research group working in Great Britain. Virginia Papaioannou, M.W. McBurney and Richard Gardner from the Department of Zoology at the University of Oxford and Martin Evans (then still working at the Department of Anatomy and Embryology at University College, London) reported preliminary results which also showed «that embryonal carcinoma cells can participate in normal embryogenesis, thus providing further evidence for the validity of the use of these cultures as a model of normal embryonic development»[99].

However, when the group published the results of their extended studies a few years later, in 1978, they were forced to question the possibility of 'normalizing' teratocarcinoma stem cells. The authors had observed in general only a limited chimaerism, and an «incomplete recovery of normal function»[100]. Furthermore, they observed an abnormal karyotype of the cell lines, and, above all, they obtained a significant number of mouse chimeras that developed tumors. These results indicated that teratocarcinoma stem cells may still be able to differentiate, but that they also undergo a change. This, of course, then became an important issue «in order to further define the validity of using cultured EC cells as a model of embryogenesis»[101]. Not only was the widespread use of EC cells as a model system for embryogenesis challenged, but the question of «reversing malignancy?»[102] had to be re-discussed.

From today's perspective, it is interesting that the published literature of that time does not reflect a long debate on these issues, which would have concerned mainly the groups in the UK and Philadelphia. One reason for this may be that the successful isolation of embryonic stem cells directly from mouse blastocysts shortly after these findings made, as Solter argues «the issue of normalcy of embryonal carcinoma

[99] V.E. PAPAIOANNOU et al., *Fate of Teratocarcinoma Cells Injected into Early Mouse Embryos*, in «Nature», 258, 1975, pp. 70-73, here p. 71.

[100] V.E. PAPAIOANNOU et al., *Participation of Cultured Teratocarcinoma Cells in Mouse Embryogenesis*, in «Journal of Embryology and Experimental Morphology», 44, 1978, pp. 93-104, here p. 102.

[101] *Ibidem*, p. 103.

[102] G.R. MARTIN, *Teratocarcinomas and Mammalian Embryogenesis*, p. 775.

cells ... irrelevant»[103]. After the first material occurrence of embryonic stem cells from mice, the «extensive use of embryonal carcinoma cells became a thing of the past»[104]. A related aspect is that a new research object, which opened up a completely new research horizon, began to emerge in the late 1970s. «The ambiguity about the nature of teratocarcinoma stem cells and their relation to other kinds of tumor cells», Martin wrote in 1980,

> «does not diminish their potential usefulness. Whether or not their ability to differentiate in vitro or in vivo represents a reversal of malignancy or normal gene expression, the cells are particularly suitable for studying mammalian development ... In addition, the production of teratocarcinoma-embryo chimeras may ultimately lead to the creation of strains of mice with novel genotypes, some of which may serve as animal models of human disease»[105].

Teratocarcinoma cells (and their use to produce mouse chimeras) were now seen as promising tools for the creation of «mutant mice at will»[106]. In the early 1980s, EC cells, as well as the newly emerging embryonic stem (ES) cells, were no longer used primarily as cellular models; rather, they became tools with which to create other organismic models, namely transgenic mice.

6. *Isolation of embryonic stem cells from mouse blastocysts in 1981*

The discussion on the similarities or even identity of EC cells and early embryo cells ongoing in the mid-1970s led, as described above, to the suggestion of two further research strategies: firstly, to produce injection mouse chimeras by using EC cells in order to prove whether or not EC cells can be «normalized»; and secondly, to try to isolate cells from the early embryo in order to compare these cells with teratocarcinoma stem cells. The latter approach involved nothing that had not been tried before. Attempts to produce *in vitro* cell cultures from early stages of the mouse embryo had been reported since the early 1960s. In a 1975 survey, Michael Sherman described the difficulties of gener-

[103] D. Solter, *From Teratocarcinomas to Embryonic Stem Cells*, p. 323.

[104] *Ibidem*, p. 323.

[105] G.R. Martin, *Teratocarcinomas and Mammalian Embryogenesis*, p. 775.

[106] *Ibidem*, here p. 209.

ating cell lines in general, and pluripotent cell lines in particular, from early mouse embryos *in vitro*. Even attempts to produce cell *cultures* from the mouse blastocyst that «proliferate or even survive beyond a few days» had failed in the 1960s[107]. Furthermore, when scientists finally succeeded in producing «long term blastocyst cultures»[108] (which contained a variety of different cell types) in the 1970s, they were still unable to isolate cell *lines* from the mouse blastocyst that showed the capacity of being pluripotent. This does not mean, however, that no cell lines existed at all. Sherman reported that several blastocyst-derived cell lines had been successfully generated at that time but none of them had behaved as pluripotent cell lines. «It is,» Sherman wrote «perhaps, unexpected that even though a variety of different cell types can be generated in long term blastocyst cultures, the embryonal-like cells do not seem to persist under our culture conditions»[109].

From a historical perspective it is interesting to note that Sherman spoke of «embryonal-like cells» when he referred to the problem of how to isolate pluripotent cell cultures from the developing embryo. What is expressed here can be described as a multiplication of referential relations: The term embryonal cell or embryonal carcinoma cell (EC) referred, as Sherman explained, to a particular cell type, namely the «undifferentiated tumor stem cells» that Stevens had obtained from mouse teratomas, in contrast to «embryonic cells», which were viewed as cells of the embryo, which «encompasses a variety of different cell species»[110]. As described in detail above, the EC cells were called «embryonal» because scientists thought of them as cells that were similar to (or even identical with) specific kinds of (pluripotent) cells in the early developing mouse embryo. When Sherman now used the expression «embryonal-like cells», this reflected reciprocal references with respect to mutual resemblances: «embryonal-like cells» were regarded as embryo cells resembling the 'embryonal carcinoma cells', which themselves had already been conceptualized as cells resembling embryo cells.

[107] M. SHERMAN, *The Culture of Cells*, p. 343.

[108] *Ibidem*, p. 344.

[109] *Ibidem*, p. 347; Sherman wrote that «shortly after attachment of the blastocyst to the culture dish, the cells of the ICM bear a striking resemblance to embryonal cells» (*ibidem*, p. 347), but attempts to culture them over a longer period failed.

[110] *Ibidem*, p. 347.

The developing embryo itself was now screened for embryonic cells that resembled the embryonal carcinoma cells in morphology and in their behavior. As we have seen, the stem cell hypothesis on cancer implied – from a theoretical point of view – that EC cells were malignant counterparts – or remains of – normal pluripotent embryo cells from the early stages of developing embryos. To prove this assumption, it was necessary to isolate materially comparable cells from the developing embryo. Therefore, at theoretical level, the intermingled concepts of «embryonal carcinoma cells» and «teratorcarcinoma stem cells» were basically defined by referring to still pluripotent cells of the early embryo. Also the related scientific hopes of using teratocarcinoma stem cells as easily available research models to perform embryological studies without embryos were grounded on this referential relation. However, in the laboratory, at the level of research practices, the referential system was turned the other way round, since stem cell-like, pluripotent embryo cells existed only in theory – or in the *in vivo* situation – but not at the level of concrete research entities such as the (today common) embryonic stem cell lines. In this situation, the embryonal carcinoma cells turned into the reference system for performing experiments aimed at the isolation of (what later became called) «embryonic stem cell lines» directly from the developing embryo. Scientists started to screen the developing embryo for material counterparts to the closely studied EC cell lines. Because of the «difficulties of identification of cell type(s)» in the «experimental situation» in which cell lineages are «being studied in isolation from the whole organism»[111], the assumed «homology», as Evans and his team wrote in 1979, «between embryonal carcinoma cells and one of the pluripotent cell lineages of the embryo» became a guideline for experiments aimed at the isolation of pluripotent cell cultures from the embryo. There were three main problems in obtaining such cell cultures: First, it was not clear at which stage in the developing embryo scientists should seek to obtain cells with pluripotent capacities; or, as Papaioannou, and her colleagues had discussed at length: what cells in the early embryo were good «candidates» for being picked out to obtain perhaps still pluripotent cells. Hence, cells from the embryo

[111] M.J. Evans - R.H. Lovell-Badge - P.L. Stern - M.G. Stinnakre, *Cell Lineages of the Mouse Embryo and Embryonal Carcinoma Cells: Forssman Antigen Distribution and Patterns of Protein Synthesis*, in N. Le Douarin (ed.), *Cell Lineage, Stem Cells and Cell Determination*, p. 115.

at a stage between the 3½ day blastocyst and the 6½ day (the so-called egg-cylinder stage) were seen as «promising sources»[112]. The second problem impeding the production of pluripotent embryonic cell lines was developing tissue culture conditions which were conducive for embryonic cells to multiply (and not to differentiate). The third problem was obtaining sufficient embryonic material, given that the early mouse embryo is a very small research object.

In 1981, Martin Evans and Matthew Kaufman (both working at the University of Cambridge) as well as Gail Martin (who after a postdoctoral stay with Evans's group in the early 1970s had returned to work at the Department of Anatomy at the University of California San Francisco) independently published two articles respectively announcing the successful «establishment in culture of pluripotential cells from the early mouse embryos»[113] and the «isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells»[114]. A specific cell culturing technique was crucial for both groups to be successful in isolating the cell lines: the use of the so-called «feeder-layers» developed by Evans's group already in the mid-1970s[115]. This method was utilized for culturing teratocarcinoma cells before. Another crucial requirement for the success of these experiments was a method developed by Matthew Kaufman (whom Evans had met no earlier than 1980) to artificially increase the size of

[112] M.J. EVANS, *Origin of Mouse Embryonal Carcinoma Cells and the Possibility of Their Direct Isolation into Tissue Culture*, in «Journal of Reproduction & Fertility», 62, 1981, pp. 625-631, here p. 629.

[113] M.J. EVANS - M.H. KAUFMAN, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, in «Nature», 292, 1981, pp. 154-156.

[114] G.R. MARTIN, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, in «Proceedings of the National Academy of Sciences», 78, 1981, pp. 7634-7638.

[115] A «feeder layer» consisted of fibroblasts that were themselves incapable of cell division but provided nutrient support. Solter emphasizes that, although the feeder layer was the crucial step that enabled isolation of the first murine embryonic stem cells; in subsequent years «it was ... shown, that for maintenance of an established culture in its undifferentiated state (ES cells are prone to spontaneous differentiation in vitro) a soluble factor identified as leukaemia inhibitory factor (LIF) was required, which then became the standard ingredient of ES cell cultures»; D. SOLTER, *From Teratocarcinomas to Embryonic Stem Cells*, p. 323.

the inner cell mass of the embryo. This method yielded sufficient cell material for experimentation[116].

Both articles argued that the cells isolated directly from the embryo behaved «in a manner equivalent to EC cells isolated from teratocarcinomas»[117], which was seen as proof that pluripotent cells had been isolated. In order to distinguish these from EC cells, Evans and Kaufman named these «directly embryo-derived cells» EK cells, where EK denoted «Evans/Kaufman»[118]. It was Martin who finally introduced the new term *embryonic stem* cells in her article of 1981:

«As demonstrated below, the cells derived from ICMs cultured in conditioned medium have all the essential features of teratocarcinoma stem cells. Such cells were termed *embryonic stem cells* (ESC) to denote their origin directly from embryos and to distinguish them from embryonal carcinoma cells (ECC) derived from teratocarcinomas»[119].

7. *Summary*

During the 1970s, embryonal carcinoma cells, as well as the entire set of experimental practices used to generate those cell lines, turned into a research model which eventually enabled scientists to isolate pluripotent stem cell lines directly from the developing mouse embryo in 1981. However, the possibility of using EC, and finally, ES cells as 'vectors' to produce mouse chimeras with controlled altered genetic information rendered largely obsolete the problem of whether or not EC or ES cells themselves could be used as model systems for the study of embryogenesis (which was the driving force behind the first isolation of embryonic stem cells in 1981). In the early 1980s, the production of chimeric mice with altered genetic information and specific mutations became a major aim of embryonic stem cell research. By applying the newly developed techniques of recombinant DNA research (such as

[116] See M. GOZLAN, *Sir Martin Evans: Leader of the Stem Cell Revolution Wins Nobel Prize (Interview)*, in «Medscape Diabetis & Endocrinology», posted 17 October 2007 (www.medscape.com/viewarticle/564324), last accessed 5 January 2012.

[117] M.J. EVANS - M.H. KAUFMAN, *Establishment in Culture of Pluripotential Cells*, here p. 155.

[118] See M. GOZLAN, *Sir Martin Evans*.

[119] G.R. MARTIN, *Isolation of a Pluripotent Cell Line*, p. 7635.

gene targeting) to the established embryological technique of producing mouse chimeras, the way was open for the creation of the first transgenic mouse models in the 1980s. In the mid-1980s, several research groups created mouse chimeras by injecting pluripotent embryonic stem cells that had been genetically manipulated *in vitro*[120]. These transgenic mice revolutionized research in medicine and biology[121]. Whereas at the beginnings of embryonic stem cell research in the 1970s, the characteristics of embryonal carcinoma cells (EC), and, concomitantly, the characteristics of embryonic stem cells (ES) were the objects of study, these cells finally turned into convenient tools for the production of transgenic mouse models. However, this was not only a shift to an application of stem cell research different from today's regenerative medicine approaches. Rather, it was a shift that also replaced theoretical considerations concerning the nature of embryonic stem cells, questions of how they differentiate and their relationship with cancer and tumor cells, and issues about the reversibility of differentiation. In 2002, the scientist Peter Andrews summarized the situation as follows:

«Although murine EC and ES cells were originally derived with approaches to addressing such questions in mind [i.e. questions about mechanisms that regulate differentiation, C.B.], most of the use of mouse ES cell technology over the past 20 years has been directed towards production of transgenic mice, and not for answering questions of fundamental cell biology pertinent to ES cells *per se*»[122].

It is interesting to see how these initial issues, which concerned both the idea of reversibility of differentiation and the question of the characteristics of stem cells themselves, seem to have returned in very recent approaches in stem cell research – in particular in the field of cellular reprogramming. The extent to which the longstanding historical debates on the relation between cancer and stem cells, as well as the scientific interpretation of stem cells as actors of both pathological and normal cell differentiation, play a role in recent discussions is of interest not just to the history of science alone.

[120] V.E. Papaioannou, *The Coming of Age*, p. 843.

[121] Martin Evans as well as Mario Capecchi (from the University of Utah, Salt Lake City) and Oliver Smithies (from the University of North Carolina-Chapel Hill) received the Nobel Prize for Medicine in 2007 for their «discoveries of principles for introducing specific gene modifications in mice by use of embryonic stem cells».

[122] P.W. Andrews, *From Teratocarcinomas*, p. 412.

The German Case

The Public Debate on Stem Cells Research in Germany

«Und bloß kein Dammbruch» / «For Heaven's Sake Avoid a Breach of the Dam»

by *Alexandra Schwarzkopf* *

I. Introduction

It should not amount to a «Dammbruch» (breach of the dam)[1]; rather «a small strictly-defined corridor»[2] should be opened for the work on stem cell research in Germany.

This was the exact formulation put forward by the German Minister of Education and Research, Annette Schavan, in her speech to the German parliament on 11 April 2008. A debate on the modification of the «old» German Stem Cell Law of 2002 was in progress. Interestingly enough, although Minister Schavan was one of the most influential proponents of the further development of the newly enacted 2008 Stem Cell Law, she seemed to have little choice but to express her reservations and warn against a «Dammbruch» on that 11 April 2008, the day of the decisive vote in parliament for a modified Stem Cell Law.

In my opinion, the fear of a «Dammbruch» – which was also expressed by other members of parliament besides Minister Schavan, and which I

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[1] Speech by Minister of Education and Research, Annette Schavan, on 4 February 2008 during the first hearing in the German Parliament on the various bills for amendment of the Stem Cell Law of 2002, Plenarprotokoll (plenary protocol) 16/142, p. 14924.

[2] Schavan's speech of 11 April 2008 during the second and third hearings in the German Parliament on the various bills for amendment of the Stem Cell Law, Plenarprotokoll 16/155, p. 16286. The plenary protocols and the printed matters of the German Parliament are available at the following internet site of the German Parliament: http://www.bundestag.de

shall henceforth call the «Dammbruchargument» – describes the entire process of the German debate on stem cell research in a nutshell.

This «Dammbruchargument» had already played an important role in the first stem cell debate from 2000 to 2002. Two so-called «mothers» of the 2002 stem cell law, Maria Böhmer and Andrea Fischer, had also used this «Dammbruchargument» in the plenary debates before the law's enactment[3]. As employed in that context, the term *Dammbruch* means «unlimited»[4] research on human embryos. In her speech of 11 April 2008 in parliament, minister Schavan pointed out that the 2002 Stem Cell Law could only obtain a majority in parliament, because (in her words) «it was clearly stated that there would be neither an incentive for the production of human embryonic stem cells for research purposes ... nor would there be any incentive for the use of human embryos»[5].

The fact that the fear of a *Dammbruch* is especially extensive and deeply felt in Germany compared with other industrial nations is definitely due to the country's negative twentieth-century political experiences. Furthermore, influences of the history of ideas also play – at least in my opinion – an important role in the German stem cell debate and the fear of a possible *Dammbruch*. Before I address specifically the public debate on stem cell research, I shall present an overview of the German laws on stem cell research.

II. Legislation on stem cell research in the Federal Republic of Germany

The relevant legislation on stem cell research in Germany is basically the German Embryonic Protection Act (Embryonenschutzgesetz, ESchG) of 13 December 1990[6] and the two German Acts for the Secur-

[3] Maria Böhmer's speech of 30 January 2002 during the hearing in the German Parliament on the different proposals as a basis for a stem cell law, Plenarprotokoll 14/214, p. 21200. Andrea Fischer's speech of 25 April 2002 during the second and third hearings in the German Parliament on bill 14/8394 for a stem cell law and the various proposals for modification, Plenarprotokoll 14/233, p. 23213.

[4] Schavan's speech of 14 February 2008, p. 14923.

[5] In her address to the German Parliament on 11 April 2008 Schavan made reference to the Stem Cell Law of 2002, p.16286.

[6] http://bundesrecht.juris.de/eschg

ing of the Protection of Embryos in connection with Importation and Use of Human Embryonic Stem Cells of 28 June 2002 and 14 August 2008. (Stem Cell Acts)[7]. The essential principle of the current German legislation is that the procurement of stem cells from early embryos is basically prohibited. Only imported stem cells may be used. Furthermore, the imported stem cells must have been procured from a previous blastocyst with a specific cut-off date. Embryonic stem cells that have been produced before 1 May 2007 (the present cut-off date) outside Germany can be imported into Germany if authorization has been issued by the Robert Koch-Institute. In contrast to the previous possible cross-border extension of the German Stem Cell Law of 2002, the modified present version of 2008 limits the application of the Stem Cell Law to Germany. Thus only the use of embryonic stem cells within Germany can be legally punishable. Due to this national limitation, stem cell researchers working in Germany cannot be held legally accountable if they work on an international stem cell project outside of Germany which would be illegal under German laws.

In summary, it should be noted that the German stem cell legislation, which is restrictive in comparison with that of other modern states, has been at least slightly liberalized through the 2008 law's amendment.

III. The general public debate on stem cell research

Various representatives of German society participated in the stem cell debate before the 2002 and the 2008 legislation was enacted. First to be considered are the members of the German parliament, who presented their points of view mainly in the Bundestag. Second to be mentioned are the scientists working in diverse disciplines who expressed their views during the hearings of the specific Parliamentary Subcommittee on Education, Science and Technical Development. Furthermore, the same experts participated in numerous councils and commissions dealing with bioethical questions. Third, scientific know-how was introduced into the debate by specific statements of the German Research Foundation (GRF) concerning stem cell research. Fourth, the churches also played an important role in a debate dealing with conflicts between such fundamental norms as human dignity, the protection of life, and

[7] http://bundesrecht.juris.de/stzg/index.html

the freedom of research, which were discussed in light of the immoral research activities and laws of the Third Reich. Fifth and finally to be mentioned is the important role performed by the media. Interestingly enough, not all the representatives of the media restricted themselves to merely reporting on the subject matter; some of them also became active participants in the German stem cell debate.

The main goal of this article is to show that the expression «Und bloß kein Dammbruch» («for heaven's sake avoid a breach of the dam») highlights the nature of the German stem cell debate. My assumption is based on both the specific content of the positions taken by the above-mentioned actors and the careful manner in which they conveyed their stances to the other participants in the debate.

1. *The protocols of the German Parliament*

By researching the protocols of the sessions of the German Parliament that dealt with the topic of stem cell legislation, one can determine that the different standpoints on embryonic stem cell research – and therefore mainly on the question of the procurement of embryonic stem cells – crossed all party lines in parliament. There was not one specific party point of view that stood out.

The sharpest critics of a liberal stem cell legislation were to be found within the Green Party and the Christian Democratic Party (CDU), but there were also opponents of a liberal stem cell legislation within the ranks of the Social Democratic Party (SPD) or the German Left Party.

Therefore, during the stem cell debate, there had been surprising coalitions of parliamentarians who stood for totally incompatible positions on most other issues. Only the delegates of the Liberals, the Free Democratic Party (FDP), were almost totally in favour of research-friendly and supportive legal regulations in the stem cell field.

On 11 April 2008 four different proposals to modify the 2002 Stem Cell Law were presented in the German Bundestag.

The first proposal (16/7981) was in favour of a one-time postponement of the cut-off date to 1 May 2007 and supported the exemption from punishment of researchers taking part in foreign research projects; the second (16/7982) demanded the elimination of the cut-off date, the third

(16/7983) supported a general ban of embryonic stem cell research; and the fourth (16/7984) advocated maintaining the present cut-off date but favoured the exemption from punishment of researchers participating in foreign scientific projects.

In contrast to all other parliamentary groups, not one of the representatives of the Green Party voted on 11 April 2008 for the most liberal bill 16/7982[8], which would have abolished the cut-off date in the Stem Cell Law; and, on the same day, Uschi Eid was the only delegate of the Green Party who voted for Bill 16/7981[9]. This provided for a one-time postponement to 1 May 2007 and exemption from punishment for researchers taking part in foreign research projects. Out of 580 votes, 346 were in favour of this bill 16/7981 – which was the one accepted in the end.

As mentioned before, the position of the majority of the Liberals on the stem cell legislation was almost the opposite of the majority position of the Greens. Whereas in the Green Party the critics of a research-supportive stem cell legislation formed the majority, the supporters of liberalization clearly made up the majority in the Liberal Party. In 2002 one of the few prominent opponents of liberalization of stem cell research within the Liberal faction was Hans-Michael Goldmann. He was the only Liberal member of parliament who voted against bill 14/8394, which envisaged the possibility of importing stem cell lines under strict conditions. Again in 2008, Goldmann was one of only five Liberal deputies out of 52 members in parliament to vote against bill 16/7981 for the one time postponement of the cut-off date. This bill received a majority in the German parliament on 11 April 2008 and became the basis of the modified stem cell law of 14 August 2008.

On the same day, during the second and third hearings on the various bills to change the 2002 Stem Cell Law, Minister Schavan of the Christian Democratic Party was given the opportunity to speak first on one of the four different proposals presented[10]. Just before the speech

8 Bundestags-Drucksache (printed matter of parliament: hereafter BT-Drs.) 16/7982.

9 BT-Drs. 16/7981.

10 On 14 February 2008 during the first hearing in the German Parliament on the various bills of a law amending the Stem Cell Law, Minister Schavan was the first speaker in the parliamentarian debate.

by the Minister for Education and Research Schavan, the President of the Parliament, Norbert Lammert, welcomed the members of the German Ethics Council as guests of the debate and pointed out that the discussion of that day on stem cell research was obviously closely connected with the Council's future duty to advise the government and parliament on ethical questions[11]. This statement by the President also emphasized the important influence of the board of experts – the German Ethics Council – in solving the conflicts between the various norms in the field of stem cell research.

Minister Schavan began her speech with the observation that

«Scientists in Germany do also have ethical convictions as we all have. They perform their work in Germany on the same basis of fundamental values that are also part of our constitution. They are not simple representatives of interests»[12].

The fact that Minister Schavan held her speech with the above-quoted words on the same day of the passage of the new Stem Cell Law emphasized the importance of the values being questioned and disputed within the German stem cell debate.

The minister's words also demonstrated her determination to achieve reconciliation between the opposing positions and contrary social groups involved. Schavan unmistakably asserted that the group of researchers favouring modification of the old stem cell law had the «same ethical convictions» in line with constitutional values as the rest of German citizens – and including the critics of stem cell research. By indicating that scientists are not simple interest-bearers without ethical convictions, she drew attention to one of the most serious accusations brought against stem cell researchers, and she declared within the same sentence that these accusations were categorically false.

Nevertheless, at the outset of her speech, Schavan sought significantly to build bridges between the different factions by emphasizing that scientists, as well as all the other proponents of low-restrictive regulations on stem cell research, respected the values of the German Constitution to the same extent as did all other citizens. Moreover, bill 16/7981, which the minister supported, should only create – as mentioned before – «a

[11] Introductory contributions to the debate in the German Parliament of 11 April 2008 by the President of the parliament Norbert Lammert, p. 16286.

[12] Speech by Schavan on 11 April 2008, p. 16286.

small, precisely defined corridor» for the work of stem cell researchers on German territory and should not be an incentive for the production and the use of human embryos. Therefore, neither a *Dammbruch* nor unlimited research was to be feared.

To sum up the 2008 speech by minister Schavan, she pleaded for a cautious «advancement» of the Stem Cell Law – and at the same time pointed out that she did not want to use the term «liberalization»[13]. In so doing, she made an effort to convince the supporters of the three other legislative proposals and she sought to gain their consensus. The Christian Democratic minister, Schavan adopted this decisive and also diplomatic way to communicate her position within the second stem cell debate because she could not even be sure that half of her colleagues in the faction would vote for the bill – which she favoured. This was the bill on the postponement of the cut-off date to 1 May 2007, which many thought had become necessary because of a growing lack of adequate stem cell lines. In 2008 the stem cell lines available in Germany, which had to have been procured before 1 January 2002, had deteriorated in quality or even become unusable because of contamination with animal products and viruses. Three hours after her speech, Schavan's fear that many of her colleagues would not support her bill was substantiated, given that more than half of her party's members decided to vote otherwise in parliament.

Also the other important participants in the political process of communication on embryonic stem cell research shared Schavan's view that in Germany there should always be respect for the dignity of human life in all stem cell research. Even the supporters of elimination of the cut-off date rule, who thereby wanted an «advancement» further than the one which Minister Schavan favoured, did not want a *Dammbruch* of unlimited research possibilities with early embryos. On 25 April 2002 the deputy of the German Left, Ilja Seifert, said during the second and third hearings on bill 14/8394 and the various proposals that it ought to be forbidden to «kill embryos for the sake of stem cell research, because we regard human dignity as untouchable. That is the highest imperative of the Constitution»[14]. During the same hearing, deputy Monika Knoche of the Green Party drew attention to the fact that the

[13] Speech by Schavan on 14 February 2008, p. 14924.

[14] Speech by Ilja Seifert on 25 April 2002, p. 23215.

«overwhelming majority of the house had left no doubt about their belief that the embryo *in vitro* has human dignity and is not disposable»[15]. Knoche was referring to the debate in parliament on 30 January 2002, in which for the first time the various group applications for a stem cell law had been deliberated. But not only those delegates who considered the import of stem cells critically cited the notion of human dignity enshrined in Article 1 Section 1 of the German Constitution as an important argument in support of their position. Also Christian Democrats like Peter Hintze, who favoured a stem cell law without any cut-off date regulation, drew on the human dignity concept. Since the aim of stem cell research is the «healing of diseases, against which we have been helpless until now», Hintze pointed out that the obligation under Art. 1 Sec. 1 of the Constitution was to «respect and protect human dignity» through «action, but also through omission»[16]. He thus implied that a stem cell law which denied «the necessary help to critically ill people» by, for example, a ban on research for the healing of diseases would also be a violation of Art. 1 Sec. 1 of the Constitution through omission.

Also in 2008, during the run-up to the modification of the 2002 Stem Cell Law, the human dignity argument once again played a central role. On 11 April 2008, during the second and third hearings on the various bills for modification of the 2002 Stem Cell Law, the Social Democrat René Röspel addressed the complex issue of human dignity. He was thereby one of the initiators of bill 16/7981, which was in favour of a one-time postponement to 1 May 2007 and promoted the exemption from punishment of researchers in violation of the German stem cell legislation while working within international research projects. This bill 16/7981 was passed with the votes of the majority of delegates just about an hour after Röspel's speech in parliament. In this parliamentary debate, Röspel had been allowed to speak just before the decisive voting on the various bills for modification of the Stem Cell Law. In his speech Röspel declared his belief that human life begins with the fusion of egg and sperm cell. However, the question of when human dignity for a human life begins had not yet been decided by society[17]. Furthermore,

[15] Speech by Monika Knoche on 25 April 2002, p. 23218.

[16] Speech by Peter Hintze on 25 April 2002, p. 23220.

[17] Speech by René Röspel on 11 April 2008, p. 16308.

Röspel raised the question as to whether one should take the chance that a researcher might not go to court to sue for permission to import a four-year-old stem cell line. He himself, Röspel continued, was not so sure that every court in Germany would grant human dignity and protection of life to such a stem cell line, which had been produced from an embryo four years previously, had been worked upon in the laboratory, had been decanted twenty times from one cell culture bottle to the other, and had been frozen and unfrozen ten times[18]. Ultimately, Röspel pleaded for not letting a court decide whether a blastocyst had human dignity, but to let the parliament make this political decision on an ethically insolvable dilemma. This should be the procedure, because this decision lay within the parliamentary and political responsibility of the delegates[19]. To be noted is that Röspel, a biologist and Chairman of the Parliamentary Advisory Board especially in the Life Sciences, differentiated between the moment of the beginning of life and the moment when this human life is granted human dignity[20]. This differentiation was made by practically all the participants in the stem cell debate who did not want to grant the embryo protection under Art. 1 Sec. 1 of the Constitution from the fusion of egg and sperm cell onwards. Hence this limitation should not be understood in the sense that the embryo in its earliest phase is totally unprotected and possibly subject to every type of use and abuse[21], even though it was not yet a possessor of human dignity.

Röspel's explanations were also significant in that he emphasized the political responsibility of the parliament to find «a stable accord» in the «ethical dilemma». This stable accord should on the one hand enable research, and on the other hand ensure the life protection of embryos. Röspel did not want the evaluation between the freedom of research protected by Art. 5 Sec. 3 of the Constitution and the protection of early embryos to be left to the judiciary. Given that he made

[18] *Ibidem.*

[19] *Ibidem.*

[20] Since April 2008 René Röspel has been Chairman of the Parliamentarian Advisory Board concerning ethical questions especially in the life sciences. Between 2002 and 2005 he also was the head of the Inquiry Commission on Ethics and Law of Modern Medicine.

[21] Speech by Petra Sitte on 11 April 2008, p. 16294.

his address just before the vote in parliament on the various bills, the emphasizing of political responsibility and therefore of the importance of the legislature can be classified as a skillful communicative device to win over Röspel's parliamentarian colleagues so that they would support the bill which he was promoting.

Not even the supporters of elimination of the cut-off date, who therefore aimed at an «advancement» even greater than the one Minister Schavan favoured, wanted a *Dammbruch* to unlimited research possibilities with early embryos. On 25 April 2002, the Christian Democrat Peter Hintze stated in a speech to the German Parliament that the intention of the new stem cell law was to give the «scientists in Germany a clear legal basis for their basic research»[22]. Hintze did not refrain from stating that the researchers had already provided for a high level of ethical responsibility[23], since they had not taken advantage of the legal possibility for import and research, but had given parliament time and space for a detailed debate and legislation[24].

These statements by Hintze show that he did not fear a *Dammbruch* in German stem cell research but assumed that scientists in Germany had carried out their research with a high level of ethical responsibility and would continue to do so in the future. These statements by a member of the Bundestag, and thus an original participant in the political process of communication on stem cell legislation, are also interesting because Hintze classified the debate by signifying it as «detailed»[25].

On 11 April 2008, also the Social Democrat Rolf Stöckel, who was one of the initiators of bill 16/7982 to eliminate the cut-off date, drew attention to the fact that no member of the German Bundestag wanted to deny the ethical consensus that not everything which is possible may be done. Furthermore, no one in the German Parliament wanted to depart from the basic principle that human life should never be exposed to «instrumentalization»[26]. Thus Stöckel stressed that he considered

[22] Speech by Peter Hintze on 25 April 2002, p. 23220.

[23] *Ibidem.*

[24] *Ibidem*, p. 23220 f.

[25] *Ibidem*, p. 23220.

[26] Speech by Rolf Stöckel on 11 April 2008, p. 16296.

the fear of a *Dammbruch* with regard to unlimited research with early embryos as unsubstantiated[27].

Thus far it seems to have been no coincidence that the predominant majority of the speeches by parliamentarians were well-balanced, sophisticatedly expressed, and substantially founded. Philosophical and ecclesiastical authorities like Immanuel Kant or Thomas of Aquinas were cited when dealing with the question of at what point in the development of human life the same constitutional dignity protection as granted to a born child should be also be granted to the developing life. On 14 February 2008 the delegate of the Liberals, Konrad Schily, referred to Kant during the debate in parliament in order to substantiate his rejection of a postponement of the cut-off date. Schily asserted that in Kant's view a human being must never just be a means but always an end in itself. This is the fundamental concept of human dignity. And this right to human dignity began, according to Schily, at the moment when the disposition to being a human arose. This is the case of the embryo[28]. Liberalizing research was a clear and unambiguous – one might also say 'progressive' – position, but this would be to disclaim human dignity[29]. The delegate of the Greens, Fritz Kuhn, who was also against postponement of the cut-off date, urged on 14 February 2008 that care should be taken with the argument which states that one must have a certain stem cell legislation because foreign states do so and because hope is linked to it[30]. This argument was a capitulation with respect to the fundamental ethical question which since Kant has been 'What may we do?'[31]. In the same debate, the Social Democrat Thomas Oppermann referred to Kant's «What can one know?» «What shall I do?» «What may I hope?» to plead for elimination of the cut-off date in order to promote basic research[32]. In Oppermann's view, stem cell

[27] *Ibidem.*

[28] Speech by Konrad Schily on 14 February 2008, p. 14898.

[29] *Ibidem.* In the same parliamentarian debate the Christian democrat Volker Kauder did also refer to Immanuel Kant: Speech by Volker Kauder on 14 February 2008, p. 14906.

[30] Speech by Fritz Kuhn on 14 February 2008, p. 14909.

[31] *Ibidem*, p. 14910.

[32] Speech by Thomas Oppermann on 14 February 2008, p. 14910.

research was basic research and consequently had the primary purpose of enlarging of knowledge[33]. Therefore, Oppermann insinuated, stem cell research was to be subjected to Kant's order: What can I know? What can one hope? Oppermann pointed out that accountable research with embryonic stem cells would yield new basic scientific findings on the development, degeneration, and regeneration of human cells. This could fundamentally enhance the life chances of future generations. Oppermann closed his speech with the remark that an enlightened person – here there is a further reference to Kant – has the right, but also the obligation, to work for this enhancement[34].

In the parliamentary debates there was an evident concern to avoid a superficial confrontation of different convictions. The delegates seemed aware of the particular gravity of the questions raised in regard to the origin of human life, freedom of research, and the ethics of healing especially in light of Germany's past political history. Jörg Hacker, the former director of the Robert Koch-Institute and Vice-President of the GRS, shares this view on the level of the parliamentary debate on stem cell research[35]. The political scientist Sheila Jasanoff of Harvard University speaks in reference to the German bioethical debate about an «extreme sensitivity to any possible state-sponsored inroads upon the sanctity of human life and human dignity»[36].

At the same time, the reference to the total scientific lack of inhibitions during the Third Reich was subtly implied rather than explicitly expressed in almost all the parliamentarians' statements. Nevertheless, it seemed to be an underlying self-evident basis for the debate. Also Simon Fink is of the opinion that the heritage of national socialism and the resulting extraordinarily intense discussion on the order of values in the German *Grundgesetz* has had great influence upon the politics

[33] *Ibidem.*

[34] *Ibidem*, p. 14911. On 11 April 2008 the delegate of the German Left Petra Sitte spoke about the danger of an «instrumentalization» of human life through a postponement of the cut-off date: Speech by Petra Sitte on 11 April 2008, p. 16294.

[35] Interview by Alexandra Schwarzkopf with Jörg Hacker on 24 November 2009 at the Robert Koch-Institute in Berlin.

[36] S. JASANOFF, *Designs on Nature. Science and Democracy in Europe and the United States*, Princeton NJ 2007, p. 159. On the general influence of the national socialist past on the German bioethical debate see *ibidem*, pp. 180-184.

of embryo research[37]. In an article on *Stem cell policies in Germany* published in 2009, Wolf-Michael Catenhusen made clear that patient support groups do not play an important role in the German stem cell debate[38]. This situation differs from that in other countries. On the other hand, the significance of alliances among the handicapped organizations with their commitment for the right to live and life protection, is considerably greater. This fact is also indubitably a legacy of national socialism and its crimes of euthanasia. Only in a few speeches did the delegates explicitly refer to the national socialism period and the crime of euthanasia. In the debate of the German Parliament on the 25 April 2002, for example, only three out of thirteen speakers referred to the Third Reich: Ilja Seifert, Monika Knoche and Wolf-Michael Catenhusen. Seifert, the delegate of the German Left who favoured a total ban on the import of stem cell lines had no problems with drawing a comparison with the Third Reich:

«We have experienced all this before. Today I have – by total coincidence – talked to the female representatives of the Bund der Euthanasiegeschädigten und Zwangssterilisierten ... They told me that it all started during the Nazi period with the Law for the Prevention of Genetically Defected Progeny. After that came the incurably and the chronically ill. Later social criteria were introduced. All of us know to what this led»[39].

During the same debate, the delegate of the Green Party, Monika Knoche, who also was in favour of a ban without exception on stem cell imports, made clear her belief that the prohibition of research for the benefit of third parties – «fremdnützig» research – is the most precious value of civilization that has been acquired from historical experiences[40]. As in Seifert's speech, the historical reference in Knoche's did not evolve logically out of the context. Knoche did not explain how research with stem cell lines could be compared with the «fremdnützig» research in the era of national socialism.

[37] S. FINK, *Ein deutscher Sonderweg? Die deutsche Embryonenforschungspolitik im Licht international vergleichender Daten*, in «Leviathan», 35, 2007, 1, pp. 107-128, here p. 124.

[38] W.-M. CATENHUSEN, *Stammzellpolitik in Deutschland*, in J.C. JOERDEN - T. MOOS - C. WEWETZER (eds), *Stammzellforschung in Europa. Religiöse, ethische und rechtliche Probleme*, Frankfurt a.M. 2009, pp. 55-73, here p. 55.

[39] Speech by Ilja Seifert on 25 April 2002, p. 23216.

[40] Speech by Monika Knoche on 25 April 2002, p. 23218.

The two above-cited statements in the German parliament highlight the extent to which comparison of embryonic stem cell research with the total lack of scientific inhibitions under national socialism is problematic. The unspoken reference to the Third Reich, which naturally weighed heavily upon the debate, and an «extreme sensitivity» to German history between 1933 and 1945, seems to be generally the more suitable and wisest way to take the experiences of the past into account for the stem cell debate. Accordingly, on 25 April 2002 the Social Democrat Wolf-Michael Catenhusen convincingly alluded to the lessons to draw from the German past. He said that one had to learn the painful lesson that scientific and technological progress does not always lead to societal progress if it is not given a direction[41].

Also in 2008, prior to modification of the 2002 Stem Cell Law, only a few participants in the debate made explicit historical references. In the decisive debate held in the German Bundestag on 11 April 2008, out of 21 delegates only Monika Knoche und Hans-Michael Goldmann referred to the past[42].

Further reasons for the restrictive German stem cell legislation in comparison with that of other industrialized nations can be found in the influences of German Romanticism and natural philosophy of the nineteenth century. Hacker, the former head of the Robert Koch-Institute and former Vice-President of the GRF, observed that German scientific-technological progress is always accompanied by the fear of an interference in nature[43]. Also one of the so-called «mothers» of the first Stem Cell Law, Margot von Renesse, spoke of the «fear of potential brutalisation in modern society»[44], and she also emphasized the «naturalness of nature»[45] as an apparent guarantee of humanity. Michael Naumann, former Minister of Culture and then co-publisher of the weekly newspaper «Die Zeit» talked in a 2001 article in the

[41] Speech by Wolf-Michael Catenhusen on 25 April 2002, p. 23221.

[42] Speech by Monika Knoche on 11 April 2008, p. 16299; speech by Hans-Michael Goldmann on 11 April 2008, p. 16300.

[43] Interview by Alexandra Schwarzkopf with Hacker on 24 November 2009 at the Robert Koch-Institut in Berlin.

[44] Speech by Margot von Renesse on 30 January 2002, p. 21196.

[45] *Ibidem.*

paper's political section about German scepticism towards natural and technical sciences and pointed out that the Federal Republic of Germany had blocked technical developments on several occasions in the course of its history[46].

The prominent stem cell researcher Oliver Brüstle[47] assumes that one way to reduce the widespread scepticism in German society concerning stem cell research is to increase and further life science education in schools and in society in general. This would certainly contribute to a more informed discussion. Having worked for several years in the US, and having collaborated on many occasions with American and British science teams, Brüstle notes that, overall, there seems to be a lower amount of 'pioneering spirit' in Germany compared with the above-mentioned countries[48].

Joachim Müller-Jung, head of the «Nature and Science» section of the «Frankfurter Allgemeine Zeitung» (hereafter «FAZ») daily newspaper has argued that one of the reasons for the extensive German stem cell debate, in which no critical demur has been left undiscussed, is the traditionally grand culture of debating in Germany[49].

2. *The statements of the scientific experts*

The oral and written contributions made by experts in the various academic fields to the hearings of the Parliamentary Subcommittee for Education, Science and Technical Development were of great importance for the German stem cell debate. This was because their views formed the bases of many speeches and decisions by German parliamentarians. Practically, all of the arguments put forward by the members of parlia-

[46] M. NAUMANN, *Der Staat und die Heiligkeit des Lebens. Bioethik ohne Gott ist möglich. Sie muss nur die Erfahrungen der deutschen Geschichte aufnehmen*, in «Die Zeit», 2001, 26, p. 10.

[47] The neuropathologist Oliver Brüstle is head of the Institute of Reconstructive Neurobiology at the University of Bonn and for at least ten years one of the most important German stem cell researchers.

[48] Interview by Alexandra Schwarzkopf with Oliver Brüstle at the Institute of Reconstructive Neurobiology at the University of Bonn on 24 February 2010.

[49] Interview by Alexandra Schwarzkopf with Joachim Müller-Jung, head of the «Nature and Science» section of «FAZ», on 19 March 2010 at the «FAZ» in Frankfurt.

ment essentially reflected the scientific contributions previously presented. Of course, due to the German past, these experts were also particularly sensitive in the stem cell debate to the protection of human life and dignity. In his written statement for the public hearing on «Modification of the Stem Cell Law» held by the Parliamentary Subcommittee for Education, Science and Technical Development on 3 March 2008, the expert on constitutional law Christian Hillgruber pointed out that the inviolability formula of Art. 1 Sec. 1 of the Constitution was a reaction of the drafters of the German Basic Law to the medical crimes of national socialism. There were consequently good historical reasons for adhering to a special German idea of dignity[50]. The Protestant theologian and bioethicist Peter Dabrock stated during the same public hearing that the 2002 Stem Cell Law had a clearly restrictive basic tenor due to German history[51]. The philosopher Robert Spaemann argued in the same hearing of the subcommittee that the healing of people should not be more important than the killing and instrumentalization of others. He went on to add that experiments on humans in the time of national socialism were justified because they would later benefit many other persons[52]. Although Spaemann did not want the reference to the Nazi period to be taken as a direct comparison, he still called it a 'structural' comparison[53].

On the other hand, there were natural and humanistic scientists who disagreed that protection of a blastocyst should be elevated to the same level of dignity protection as given to a born child by Article 1 Sec. 1 of the German Constitution. During the public hearing on the

[50] Christian Hillgruber in his written statement for the public hearing on «Modification of the Stem Cell Law» held by the parliamentary Subcommittee for Education, Science and Technical Development on 3 March 2008, Ausschussdrucksache (printed matter of the Subcommittee, hereafter A-Drs.) 16 (18) 336a, p. 5. The printed matters of the Subcommittee can only be read at the Subcommittee for Education, Science and Technical Development. I would like to thank Ministerialrat Andreas Mayer for his help in enabling me to research the hearing protocols and the written statements of the experts.

[51] Peter Dabrock during the public hearing on Modification of the Stem Cell Law held by the parliamentary Subcommittee for Education, Science and Technical Development on 3 March 2008, Bundestagsprotokoll (protocol of the parliament) 16/53, p. 6.

[52] Robert Spaemann during the public hearing on 3 March 2008, p. 8.

[53] *Ibidem*, p. 9.

topic «Stem Cell Research» held by the Parliamentary Subcommittee for Education, Science and Technical Development on 9 May 2007, the constitutional scholar Friedhelm Hufen indicated that the German Supreme Court had not yet ruled on the bearing of human dignity in the era of pre-nidative life, not even in its two rulings on abortion[54]. The professor of criminal law and legal philosophy, Reinhard Merkel, explained in his written statement to the same public hearing that the large majority of the moral philosophers involved in the international discussion distinguished between the ethical obligations towards the earliest forms of human life and towards later born life. They considered the obligation to the unborn child to be of far less weight[55]. On the other hand, Hillgruber made the following remark during the public hearing held on 3 March 2008: The Supreme Court has pointed out in its two judgements concerning abortion that «in any case» – this is the literal formulation of the Supreme Court – from the moment of nidation onwards the foetus has human dignity. Hillgruber continued by claiming that this ruling by the Supreme Court was in fact more a reasoning to grant human dignity from the fusion of egg and sperm cells onwards. Hillgruber assumed that the formulation «in any case from the moment of nidation onwards» spoke for this interpretation[56]. In fact, the Supreme Court had not yet explicitly ruled that the moment of the fusion of egg and sperm cell was the beginning of human dignity. Hillgruber omitted to comment on this contradiction of his view.

Independently from the question of the human dignity of a blastocyst, many experts pointed out that the central issue for the stem cell legislation was the importing of stem cell lines, not the importing of embryos. In the prior hearing of 9 May 2007, Hufen pointed out that the Supreme Court's so-called «object formula», which declares that a human being is deprived of his/her humanness if s/he is treated as an object, amounts to a violation of Art. 1 Sec. 1 of the Constitution and can only be applied to research with embryos, not to research with

[54] Friedhelm Hufen during the public hearing on the topic «Stem Cell Research» of the parliamentary Subcommittee for Education, Science and Technical Development held on 9 May 2007, Bundestagsprotokoll 16/34, p. 77.

[55] Written statement of Reinhard Merkel to the public hearing on the topic «Stem Cell Research» of the Parliamentary Subcommittee for Education, Science and Technical Development held on 9 May 2007, p. 3, A-Drs 16 (18)1930.

[56] Christian Hillgruber during the public hearing on 3 March 2008, p. 51.

stem cell lines. Hufen also maintained that application of the «object-formula» to embryo research required in the first place that this research should effectively violate the ban on instrumentalization, and was thus a violation of human dignity[57]. Also the expert on medical law, Jochen Taupitz, stated on 9 May that the Stem Cell Law only dealt with the use of stem cells, not with the use of embryos[58]. During the hearing of the subcommittee held on 3 May 2008 Taupitz insisted:

«The research with embryonic stem cells – for the sixth or seventh time; this has already been stressed by several experts – is not about the life protection or human dignity of living embryos but about derivates, about subsequent actions»[59].

Moreover, other legal contradictions in the German law concerning unborn life were discussed in light of the fact that the Embryonic Protection Act of 1990 forbids the procurement of stem cells from a blastocyst because the latter would be killed by this procedure. This law is surprising, since the German law does not grant developing human life the same protection as born life – not even after the moment of nidation. In fact, the German law considers that the protection of developing life must under certain restrictive circumstances be weighed against other superior interests, such as the potential to heal the sick. This is evident both in the fact that the type of contraception which hinders nidation is legal and in the fact that an abortion can be performed without legal consequences up to the twelfth week of pregnancy, even if there is no medical justification for the abortion. In the case of a medical justification, an abortion is legal practically until the end of the pregnancy[60]. During the hearing of 3 March 2008, the delegate of the German Left Knoche explained this basic difference between the protection of the blastocyst «in vitro» and «in vivo»: The embryo «in vivo» enjoys the protection of the mother and exists in her body. It is protected against outside interference and is not accessible to instrumentalization. By contrast, the embryo «in vitro» is created

[57] Friedhelm Hufen during the public hearing on 9 May 2007, p. 77.

[58] Jochen Taupitz during the public hearing on 9 May 2007, p. 95.

[59] Jochen Taupitz during the public hearing on 3 March 2008, p. 30.

[60] J.N. NEUMANN, *Das Kreuz mit den Argumenten. Schwangerschaftsabbruch, Reproduktionsmedizin, Stammzellforschung und die Frage nach dem moralischen Status des Embryo*, in J.C. JOERDEN - T. MOOS - C. WEWETZER (eds), *Stammzellforschung in Europa. Religiöse, ethische und rechtliche Probleme*, Frankfurt a.M. 2009, pp. 211-241, here p. 212.

through humans and exists as a member of humankind in society[61]. The argument most commonly used to justify the diverse levels of protection is the following: in the case of the blastocyst within the womb, the well-being of the mother is to be weighed against the right to live of the blastocyst; whereas with a blastocyst *in vitro* no rights of the mother can be weighed against the right to live of the blastocyst.

In spite of these attempts to explain the diverse levels of protection, it is evident that the German legislator does not grant unborn life protection comparable with that given to born life, but considers it to be weighed in the best interest of one or other. Therefore, especially during the first controversial stem cell debate, the question arose as to whether the protection of a superfluous blastocyst obtained from in-vitro-fertilization, and which would be disposed off sooner or later, was more important than use of the blastocyst for the possible healing of a person with a harmful or deadly medical defect[62]. In the second debate, the main subject of discussion was the contradiction between the Embryonic Protection Act and the 2002 Stem Cell Law. Because of the ban on the production of stem cell lines on German territory imposed by the Embryonic Protection Act, there was obviously a serious contradiction within the German legislation on stem cell research. On the one hand, scientists in Germany were allowed to use imported stem cell lines; on the other, the procurement of them was strictly legally forbidden[63].

As stated before with regard to the speeches by parliamentarians, also the level of the specialists' contributions to the subcommittee's hearings should be emphasized. The chair of the subcommittee hearing held on 9 May 2007, the delegate Ulla Burchardt, evaluated it as a highlight in the specialist consulting of the subcommittee[64]. In her view, the contributions were of high excellence, precision, and detailedness[65].

[61] Monika Knoche during the public hearing on 3 March 2008, p. 35.

[62] K.M. SIKORA, *Biopolitik und politische Kommunikation. Die Rolle der Bundesregierung in der Stammzellendebatte*, Stuttgart 2006, p. 92.

[63] K. HILPERT, *Fünf Jahre deutsches Stammzellgesetz*, in «Stimmen der Zeit», 226, 2008, 1, pp. 15-25, here p. 20.

[64] Ulla Burchardt during the public hearing on 9 May 2007, p. 105.

[65] *Ibidem*, p. 106.

The experts' oral and written statements contained references to such philosophical and ecclesiastical authorities as Kant and Thomas of Aquinas. The Catholic theologian, Matthias Beck, stated during the subcommittee hearing of 9 May 2007 that in «our» philosophical view, as shaped by Immanuel Kant, the embryo should not be totally instrumentalized. It should not be used for purposes entirely outside itself[66]. The legal scholar and philosopher Merkel pointed out that his «honoured colleague» Beck should not cite Immanuel Kant for his human dignity justification of the embryo because it was Kant who has founded human dignity on autonomy – on the ability of the person autonomously to self-decide his or her life-issues[67]. On the other hand, Spaemann pointed out on 3 March 2008 that human dignity in Kant's sense implies that it cannot be weighed against other superior interests. Rather, human dignity means that every human being is the bearer of rights[68]. During the same hearing, the Catholic theologian Konrad Hilpert explained that, in the history of theology, the question of the exact beginning of life has for at least 700 years, until the last third of the nineteenth century, been left up to the theologians to determine. There were two positions: the one which is favoured today; and the one which saw ensoulment within a gradual development[69]. Peter Dabrock argued that, in Thomas of Aquinas' opinion, it could not be said that there is a complete soul within the sperm from the beginning[70]. Moreover, Dabrock stated that also Albertus Magnus, the teacher of Thomas of Aquinas, had held this view[71].

Even if the communication among the different qualified participants in the debate was largely based upon mutual respect, given the high level of the legal interests and principles involved, harsher tones were sometimes used. On 3 March, the molecular biologist Hans R. Schöler reprimanded the Christian Democratic delegate Hubert Hüppe because

66 Matthias Beck during the public hearing on 9 May 2007, p. 51.

67 Reinhard Merkel during the public hearing on 9 May 2007, p. 68.

68 Robert Spaemann during the public hearing on 3 March 2008, p. 9.

69 Konrad Hilpert during the public hearing on 3 March 2008, p. 16.

70 Peter Dabrock during the public hearing on 3 March 2008, p. 46 f.

71 *Ibidem*, p. 47.

he had publicly questioned Schöler's credibility[72]. During the same hearing, Dabrock declared that the destruction of embryos can be equated with the importing of embryonic stem cell lines on neither legal nor moral nor ethical grounds. To do so would, in his estimation, be a deliberate simplified cover-up[73]. Although Dabrock refrained from giving the names of those whom he reproached for this cover-up, his comment indicates that discussion among the participants in the debate was not always particularly polite. This observation is supported by Schöler's final statement in his last speech on 3 March: «If I saw a 'slippery slope', then it would be the one that, when we meet the next time, we will talk about creationism and such things as whether evolution has really occurred»[74]. It is significant that no such comments by representatives of contrary positions were made on 11 March 2002, during the public hearing of the Parliamentary Subcommittee for Education, Science and Technical Development. This seems to be symptomatic of the fact that during this debate, in contrast to the two subcommittee hearings of 2007 and 2008, the «big questions» such as the beginning of life, the protection of human dignity, the prohibition of instrumentalization, and especial sensitivity because of the total lack of scientific inhibitions during the Third Reich were practically not raised. This is quite remarkable, because the debates in the German Bundestag in 2002, and especially the statements by the councils, commissions, churches as well as the media, devoted even more time and space to the fundamental questions concerning stem cell research than they did in 2008. By contrast, the hearing of experts on 11 March 2002 concentrated mainly on detailed questions to do with individual paragraphs in the bill. On that day, besides scientific information, questions like the following were discussed: Should the restricted import of stem cell lines be allowed rather than the restricted import of individual stem cells?[75]. Who should be part of the Central Ethics Commission (CES) at the Robert Koch-Institute?[76].

[72] Hans R. Schöler during the public hearing on 3 March 2008, p. 34.

[73] Peter Dabrock during the public hearing on 3 March 2008, p. 25.

[74] Hans R. Schöler during the public hearing on 3 March 2008, p. 53.

[75] The biologist, Peter Gruss, during the public hearing on the Stem Cell Law held by the parliamentary Subcommittee for Education, Science and Technical Development on 11 March 2002, Bundestagsprotokoll 14/62, p. 26

[76] Jochen Taupitz during the public hearing on 11 March 2002, p. 30.

What kind of discretionary scope can the CES exercise over the vote of the National Ethics Council?[77]. Should the parents or other empowered persons give their consent to the use of embryos for stem cell research?[78]. On 11 March 2002 the constitutionality of a cut-off regulation, with regard to a possible violation of the principle of freedom of research (guaranteed in Art. 5 Sec. 3 of the Constitution), was practically the only constitutional topic considered[79]. Of course, the just-stated observations concerning the hearing of experts on 11 March 2002 are not to be misinterpreted as showing that the experts and delegates did not have clear notions about the «big questions» associated with the stem cell issue. Their concern with these «big questions» is evidenced by the written statements made to the hearing of 11 March 2002[80]. The observations related to this hearing may be interpreted in the following way: only a month before the decisive vote in parliament on the first Stem Cell Law, the need to deal with specific questions of the law was more pressing than on the occasion of the 2007 and 2008 hearings on modification of the Stem Cell Law.

3. *The statements and recommendations of the councils and committees*

On the basis of the statements and recommendations of the various councils and commissions concerned with bioethical questions in Germany, and which also wanted to prevent a «breach of the dam», the members of parliament could also draw up a clear and balanced picture of the various norms conflicting with stem cell research.

In the November 2001 foreword to the interim report on stem cell research, Margot von Renesse, the chairwoman of the Inquiry Commission on Law and Ethics in Modern Medicine created by the German

[77] Martin Pagenkopf during the public hearing on 11 March 2002, p. 42.

[78] The former President of the Supreme Court, Ernst Benda, during the public hearing on 11 March 2002, p. 46.

[79] Jochen Taupitz during the public hearing on 11 March 2002, p. 51, The former president of the Supreme Court, Ernst Benda, during the public hearing on 11 March 2002, p. 58.

[80] About the human dignity problematic within stem cell research: The constitutional scholar, Wolfgang Löwer, in his written statement to the public hearing on 11 March 2002, A-Drs. 14-574 l , pp. 2-4; Reference to Kant: The ethicist, Thomas Heinemann, in his written statement to the public hearing on 11 March 2002, A-Drs., 14-574 h, p. 1.

Parliament in May 2000 confirmed that the committee's experts have given competent advice to the delegates[81]. The experts had therefore adapted to the parliamentarians' manner of thinking and debating[82].

Furthermore, besides their informative functions, the councils and commissions had another important function – that of pacification. With their moral integrity and authority, the Inquiry Commission on Law and Ethics in Modern Medicine, the National Ethics Council, succeeded by the German Ethics Council, and the Central Ethics Commission for stem cell research at the Robert Koch-Institute (CES) were empowered to conciliate the opposing positions in the stem cell debate. Von Renesse referred to this in the foreword to the interim report of the Inquiry Commission as follows: With the interim report the Inquiry Commission does not only provide the parliament with an overview on the actual, factual proceedings and the present stage of discussion but also offers a method with which to achieve mutual trust, maybe even a compromise[83].

It should be noted that some sceptics initially denied that the National Council had the integrity and authority for mutual confidence building. It had been created on 2 May 2001 by the Gerhard Schröder government. The Council was composed of twenty-five well known and respected personalities from the various fields of science, politics, society, and the churches. It was intended to be a national forum for dialogue on ethical questions in the life sciences. From its inception, the National Ethics Council had to deal with the accusation that it had been created to legitimize Chancellor Schröder's liberal position on stem cell research. In retrospect, however, it is evident that the members of the Ethical Council «could not have been swayed» but brought differing positions into the public debate[84]. In its first statement *On the Import of*

[81] The Inquiry Commission consists contrary to the National Ethics Council of 26 members with equal representation of delegates and non delegates.

[82] Second interim report of the Inquiry Commission on «Law and Ethics of modern Medicine», part-report on stem cell research, November 2001, BT-Drs., 14/7546, pp. 1-88, here p. 5.

[83] *Ibidem.*

[84] This is also the perception of Joachim Müller-Jung, the head of the *Nature and Science* section of the «FAZ»: Interview by Alexandra Schwarzkopf with Joachim Müller-Jung in Frankfurt on 19 March 2010.

Human Embryonic Stem Cells[85] issued in December 2001, the National Ethics Council, which contrary to the Inquiry Commission consisted only of non- parliamentarians, described its function in the following way: The Council has the mandate to comment on ethical questions raised by new possibilities and developments within the life sciences and which need public clarification[86]. The Ethical Council is expected to deliver statements for political and legislative acts. In a democratic society this includes public dialogue[87]. This official statement by the Council shows that the Council, like the Inquiry Commission, wanted to promote «understanding» and «public dialogue».

The foreword to the Inquiry Commission's interim report on stem cell research stated that the report sets out the positions in German society and in the Inquiry Commission concerning the ethical and legal aspects of stem cell research just as extensively[88]. The different courses of action were elaborated with propositions and arguments in order to aid members of parliament to make their own judgements[89]. The aim of the Inquiry Commission to provide parliament with an «all-embracing ethical and legal evaluation of stem cell research» was probably the main difference with respect to the intent of the National Ethic Council. Whereas it was most important for the Inquiry Commission to provide parliament with comprehensive information, apparently more important for the National Ethics Council, besides its informative function, was to provide an impetus for political and legislative actions. Therefore, it is no coincidence that the information on how many members of the Inquiry Commission chose which legal regulatory option is given in the middle of the report, whilst the Ethics Council gave information on voting by its members a prominent position at the end of its report. With regard to contents, the majority of the Inquiry Commission argued

[85] National Ethics Council: About the import of human embryonic stem cells. Statement, December 2001, pp. 1-59, here p. 47: http://www.ethikrat.org/dateien/pdf/Stellungnahme_Stammzellimport.pdf

[86] National Ethics Council: About the import of human embryonic stem cells. Statement, December 2001, p. 7.

[87] *Ibidem.*

[88] Second interim report of the Inquiry Commission on «Law and Ethics of modern Medicine», part-report on stem cell research, November 2001, p. 5.

[89] *Ibidem.*

against making it legally possible to import embryonic stem cells under strict conditions. Contrary to this position, the majority of the National Ethics Council favoured such a regulation.

Furthermore to be noted is that the Inquiry Commission's report was much more extensive and detailed and had an academic «textbook character». Instead, the National Ethics Council's statement was more a basic position paper on ethical questions connected with stem cell research.

Thanks to the existence and functioning of the various councils and commissions, the discussions in general society were more or less already appeased by the first stem cell law in 2002. The councils and commissions stand out for the almost exemplary process of the German debate on stem cell research; 'exemplary' not only because of the high level of the contributions but also because of their balanced approach to communicating and to compromising.

Also the work of the CES, the Central Ethics Commission for stem cell research at the Robert Koch-Institute, has had a pacifying influence on the German stem cell debate. Since 2002 it has been required by law that the CES must provide a position paper as a precondition for the issue of a permit for the import of stem cell lines. The permit itself can then be issued by the Robert Koch-Institute as the appropriate government agency. The CES is an interdisciplinary commission whose eighteen members are experts in ethics, theology, biology and medicine. They examine applications on the basis of the Stem Cell Law with regard to the high priority of the research objectives, the sufficient preliminary examination of the research project and the anticipated need to use human embryonic stem cells[90].

It should be noted that between 2002 and 2009 the CES authored 55 statements, which in 53 of cases led to the approval of stem cell imports without a public discussion or criticism of any of these permits. The specifications of the imported human embryonic stem cells and the basic data on the research projects approved by the RKI (as the responsible government agency) are kept in a publicly open register[91].

[90] http://www.rki.de/cln_160/nn_197444/DE/Content/Gesund/Stammzellen/ZES/zes-inhalt.html?__nnn=true

[91] http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register__node.html

One should also impute to this board of experts a pacifying influence upon the debate[92].

Also to be noted is that the appointment alone of these diverse councils and commissions clearly demonstrates the importance given in Germany to preventing a *Dammbruch* in the field of embryonic stem cell research.

4. *The statements of the German Research Foundation*

The statements of the German Research Foundation, as the central voice of science in Germany, were of great importance for the German stem cell debate. This is because the German Research Foundation gave the decisive impetus to the German stem cell debate which led to the enactment of the Stem Cell Laws. This impetus by the Research Foundation consisted in interruption of the permission procedure caused by Oliver Brüstle's application to import embryonic stem cells in August 2000. The aim was to give the lawmakers a chance to create a specific law on stem cells aside from the existing Embryonic Protection Act of 1990. In May 2001 the German Research Foundation itself for the first time argued explicitly in favour of the import of stem cells[93].

This statement stands in contrast to the GRF's first statement on stem cell research issued in 1999, which called for a debate on the stem cell issue. The opinion-forming process should take place on a broad societal basis with the active participation of the GRF[94]. Moreover, at the end of 2006 the GRF, with its third position paper on stem cell research, again had a crucial impact on the debate by requesting elimination of the cut-off date and restriction of the application of the Stem Cell

[92] On this influence of the CES see also S. SPERLING, *Converting Ethics into Reason: German Stem Cell Policy between Science and the Law*, in «Science as Culture», 17, 2008, 4, pp. 363-375.

[93] Empfehlungen der Deutschen Forschungsgemeinschaft zur Forschung mit menschlichen Stammzellen, 3. Mai 2001, pp. 3-7, here pp. 3 ff. http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/download/empfehlungen_stammzellen_03_05_01.pdf

[94] DFG-Stellungnahme zum Problemkreis Humane embryonale Stammzellen, März 1999, pp. 1-6, here p. 6. http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/archiv_download/eszell_d_99.pdf

Law to Germany[95]. One can even say that modification of the German Stem Cell Law has been – within the framework of the borders of the dam – promoted mainly by representatives of the sciences, and not by politicians or representatives of the church[96]. The latter two groups seem to have feared that another debate on stem cell issues might lead to changes to the legal rules which those groups feared.

5. *The role of the churches*

It is not particularly surprising that the various statements and press releases by the Council of the Protestant Church in Germany and by the Catholic German Bishops' Conference, as well as the communiqués of important individual churchmen – like Cardinal Karl Lehmann or the Chairman of the Council of the Protestant Church in Germany, and thus the head of the Protestant Church, Präses Manfred Kock – supported the basic position of «Und bloß kein Dammbruch», because the churches advocate the total protection of life from the fusion of egg and sperm cell onwards.

On 30 January 2002, the German Bishops' Conference published a press release occasioned by the German Parliament's decision on the importing of human embryonic stem cells. The then head of the Bishops' Conference, Cardinal Karl Lehmann, and the Chairman of the Council of the Protestant Church, Präses Manfred Kock, expressed great disappointment at the German Parliament's decision to allow the import of human embryonic stem cells – even under strict conditions. With this decision, the right to life and its unlimited protection from the moment of fertilization onwards was no longer guaranteed[97]. This assertion clearly demonstrates that the two Christian churches in Germany consider

[95] DFG-Stellungnahme: Stammzellforschung in Deutschland – Möglichkeiten und Perspektiven, Oktober 2006, pp. 1-81, here p. 8; http://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/2006/stammzellforschung_deutschland_lang_0610.pdf

[96] K. HILPERT, *Fünf Jahre deutsches Stammzellgesetz*, in «Stimmen der Zeit», 226, 2008, 1, pp. 15-25, here p. 16.

[97] Press release by the German Bishops' Conference on 30 January 2002 about the decision of the German Bundestag concerning the import of human embryonic stem cells. All press releases of the German Bishops' Conference are to be found at their internet site: http://www.dbk.de/

the embryo to be a human being right from the moment of fertilization. The press communiqué continued by requesting all politically responsible persons to insist upon the protection of human life from the outset notwithstanding the decision of the Bundestag, in order that this decision did not lead to a «breach of the dam»[98]. The expression «breach of the dam» was thus used by the churches as well! In July 2006, The German Bishops' Conference sharply criticized the decision of the European Council of Ministers on the 7th European Research Framework Programme from 2007-2013, because it included promotion of «the use and elimination of the embryo for research purposes»[99]. Also the Protestant Church of Germany spoke out against the decision of the European Ministers of Research. However, a press release from the Chairman of the Protestant Church, Bishop Wolfgang Huber, on 25 July 2006 expressed «regret» about this decision, rather than «sharp criticism»[100]. The fact that this criticism of decisions connected with the stem cell was made by the Protestant Church in somewhat more moderate terms than the criticism by the Catholic Church is rather symptomatic.

The position of the Christian Churches in Germany in regard to the total protection of life from the fusion of egg and sperm cell onwards is not surprising. However, this conviction on the initial starting-point of life, and therefore its protection, is not generally adhered to by other important religions like Islam and Judaism.

Remarkable within the process of debate and communication was the statement of 10 November 2006 by the then head of the Protestant Church, Bishop Huber, in which he declared that he could respect a one-time postponement of the cut-off date as a serious attempt to find a balance and pacify ethical conflicts. The balance between the oppos-

[98] Press release by the German Bishops' Conference on 30 January 2002 about the decision of the German Bundestag concerning the import of human embryonic stem cells.

[99] Press release by the German Bishops' Conference on 24 July 2006: Schwere Niederlage für den Embryonenschutz in Europa.

[100] Press release by the Protestant Church in Germany on 25 July 2006: *EKD Ratsvorsitzender bedauert Entscheidung der EU-Forschungsminister zur embryonalen Stammzellenforschung.* All press releases from the Protestant Church in Germany are to be found at their internet site: http://www.ekd.de/

ing ethical convictions, which the German Parliament was striving to achieve, would remain in place if the cut-off date was newly established. It would therefore have to be a past cut-off date. From the Protestant perspective, the fundamental ethical considerations against the use of human embryos to produce human embryonic stem cells would not be dispelled. Nevertheless, such a solution could be respected as a serious attempt to find a balance and to pacify the ethical conflicts[101]. Four years previously, on 22 February 2002, the Council of the Protestant Church had released a press report which stated that the Council of the Protestant Church in Germany respected the attempt of the German Bundestag to strike a balance between the opposing convictions and thus reconcile the ethical conflict in the legal order[102]. With regard to analytical aspects of communication, it is interesting that the «personalized» statement of Bishop Huber in 2006 had a much greater impact on the German stem cell debate than the press release by the Council of the Protestant Church in 2002. This position taken by Huber on 10 November 2006 provoked repudiation not only within the Catholic Church but also within the Protestant Church. Furthermore, it was the beginning of a split in the unanimous position on bioethical questions hitherto adopted by both of the major German churches[103]. Nevertheless, Bishop Huber's position did not at all question the «Und bloß kein Dammbruch»-fear. Interestingly enough, within the same statement of 10 November 2006 Huber clearly and decisively opposed the German Research Foundation's call for abolition of the cut-off date, which was published on the same day[104]. On 14 November 2006, just four days after Huber's exceptional statement, the German Chancellor

[101] Press release by the Protestant Church in Germany on 10 November 2006: *Erklärung des Vorsitzenden des Rates der Evangelischen Kirche in Deutschland (EKD), Bishop Wolfgang Huber, zur Stellungnahme der Deutschen Forschungsgemeinschaft (DFG) «Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland».*

[102] Press release by the Protestant Church in Germany on 22 February 2002: *EKD-Rat: Restriktionen für Stammzellen-Import nicht aufweichen.*

[103] W.-M. CATENHUSEN, *Stammzellpolitik in Deutschland*, in J.C. JOERDEN - T. MOOS - C. WEWETZER (eds), *Stammzellforschung in Europa. Religiöse, ethische und rechtliche Probleme*, Frankfurt a.M. 2009, pp. 53-73, here p. 69.

[104] Press release by the Protestant Church in Germany on 10 November 2006: *Erklärung des Vorsitzenden des Rates der Evangelischen Kirche in Deutschland (EKD), Bishop Wolfgang Huber, zur Stellungnahme der Deutschen Forschungsgemeinschaft (DFG) «Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland».*

Angela Merkel and Minister Schavan adopted Huber's position in a discussion between their Christian Democratic Party and the Council of the Protestant Church[105].

Huber himself responded to the criticism of his position by arguing that a categorical rejection of all research on embryonic stem cells, as insisted upon by the Catholic Church, was easier to justify but it could hinder responsible results[106]. The press release by the German Bishops' Conference on 30 January 2002, which has already been discussed above, also contained a highly interesting comment on the level of the parliamentarians' contributions. The delegates were thanked for having participated with great seriousness in the debate on this difficult ethical question[107]. The formulation «we thank» indicates the Churches' self-perception of their role in the bioethical communication process as that of a superordinate critical and moral observer. This self-perception is even clearer in the last sentence of the press release: «We will remain watchful concerning the bioethical decisions to come and will call attention to possible hazards»[108]. Also the Council of the Protestant Church in Germany expressed its appreciation of the communicative manner of the delegates in 2002. The highest representative body of the Protestant Church, like the German Bishops' Conference, thus selected the sovereign formula of «one thanks». The Council thanks the delegates for a debate in which the different convictions have been expressed with reciprocal respect[109]. Furthermore, in the same press release the Council of the Protestant Church commented on the contributions to the debate by the experts, confirming that they had led to respect for, and trust in, researchers even if they had reached other ethical conclusions[110]. Bishop Huber said in his statement of 10 November

[105] W.-M. CATENHUSEN, *Stammzellpolitik in Deutschland*, here p. 70.

[106] Press release by the Protestant Church in Germany on 12 February 2008: *Für Lockerung der Stammzellforschung.*

[107] Press release by the German Bishops' Conference on 30 January 2002: *Zur Entscheidung des Deutschen Bundestages über den Import menschlicher embryonaler Stammzellen.*

[108] *Ibidem.*

[109] Press release by the Protestant Church in Germany on 22 February 2002: EKD-Rat: *Restriktionen für Stammzellen-Import nicht aufweichen.*

[110] *Ibidem.*

2006 that the GRF's statement of the same day deserved and required careful consideration: «In the view of the Protestant Church it has to be determined whether the GRF has put forward aspects which will cause us to revise our position on stem cell research»[111]. This statement shows that some members of the Church were willing to listen to and be influenced by other participants in the process of political communication on the stem cell issue. Some church representatives, for instance Bishop Huber, referred in their contributions to philosophical authorities like Immanuel Kant. In a speech given on 28 January 2002, Huber said that the notion of human dignity stands for circumstances of mutual acceptance in which (to put it with Kant's famous formula) the humanity of each human being should never be accepted and respected only as a means but always as an end in itself[112].

6. *The role of the media*

Another very important influential factor was the broad impact of the media in all areas of the German stem cell debate. Interestingly enough, in some cases the role of some media representatives went beyond that of simple mediation between the political actors and the public. Some media representatives, in fact, did not restrict themselves to reporting alone. For example, Frank Schirrmacher, one of the publishers of the «FAZ», gave the debate extensive coverage in the newspaper, especially before the first stem cell legislation. He also became a widely recognized critic of embryonic stem cell research. His position, too, was the typical «Und bloß kein Dammbruch»-stance. On 3 May 2001, Schirrmacher and his colleagues at «FAZ», Patrick Bahners and Christian Geyer, conducted an interview with the then Chancellor Gerhard Schröder on biopolitics and the National Ethics Council, which had been created by Schröder's cabinet just one day before[113]. After only a few questions, and

[111] Press release by the Protestant Church in Germany on 10 November 2006: *Erklärung des Vorsitzenden des Rates der Evangelischen Kirche in Deutschland (EKD), Bischof Wolfgang Huber, zur Stellungnahme der Deutschen Forschungsgemeinschaft (DFG) «Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland».*

[112] Press release by the Protestant Church in Germany on 28 January 2002: *Menschenwürde und Forschungsfreiheit. Wolfgang Huber anlässlich des Bioethik-Kongresses in Berlin.*

[113] P. BAHNERS - C. GEYER - F. SCHIRRMACHER, *Die Notwendigkeit der Abwägung stellt sich immer wieder neu. Im Moment muß man das Embryonenschutzgesetz nicht ändern:*

after the journalists had expressed their interpretation of the German Supreme Court's opinion on the beginning of human dignity, it became clear that their position on bioethics was different from that of the Chancellor. The questions and comments of the three journalists could not be specifically attributed to any one of them, because they spoke collectively for the «FAZ». Schröder reacted to their critical remarks on bioethics aggressively and in some cases even with annoyance. The Chancellor countered their interpretation of the Supreme Court's view on the beginning of human dignity thus:

«If you carefully considered the rulings of the Supreme Court ... you would realize that the main principle (*Leitsatz*) in both decisions to which you refer in its absoluteness is not even adhered to by the Court itself».

Thereupon the «FAZ» responded:

«Still the burden of justification lies with the person who pursues the 'instrumentalization of the embryo' ..., and not the reverse. The question remains as to how the elimination of a bearer of human dignity ... could be justified in the court».

The formulation «instrumentalization of the embryo» with reference to the use of superfluous embryos for the production of stem cells evidences the critical position of the «FAZ» and therefore of Frank Schirrmacher.

Furthermore, the Chancellor expressed his desire for a «public discussion on these questions, which should be somewhat broader and should not only occur in the cultural section (*Feuilleton*) of the FAZ». This overt jab at the journalists Chancellor Schröder could not resist.

The mode of communication between the journalists and the Chancellor was confrontational from the outset. At no point in the interview did there seem to be a possibility that one side would reconsider its attitude towards the bioethical questions considered because of the other side's arguments. Both participants in the communication used the medium of the prestigious newspaper to present their positions. The fact that Chancellor Schröder used it thus is less surprising than the fact that the journalists did so. For good reason Schröder explicitly described this interview as a conversation – not as an interview.

Also other remarks by Schirrmacher demonstrate his critical and worried attitude towards the new possibilities in the «biotechnical

Ein Gespräch mit Bundeskanzler Gerhard Schröder über die Biopolitik und den Ethikrat, in «FAZ», from 3 May 2001, pp. 56-57.

age»[114]. Only a few weeks after the just-mentioned interview with the Chancellor, an article by Schirrmacher was published in the «FAZ» cultural section: *Privatschule des Lebens. Der Embryo im Zeitalter Gerhard Schröders*. Schirrmacher wrote:

«Instead of using embryos, politicians should prepare the general society for the fact that the gene-age will dramatically alter the relationship between parents and children ... It is not the persons who declare the fertilized egg cell to be a human being who are fundamentalists, but rather those persons who already individualize the embryo by means of selection. The dictatorship of the individual as a dictatorship over biology – ten years ago nobody would have dreamt of this variant of Marxism. Rarely have ethical questions been such radical biological questions»[115].

Regardless of whether one shares Schirrmacher's position or whether one regards it as too severe, there is no doubt that already a decade ago he was among the first to recognize the fundamental changes ongoing in the «gene-age»[116] and that he made a crucial contribution to the path-breaking bioethical discussion in Germany. Already in 2000, on the occasion of the expansion of one of the British laws on therapeutic cloning, Schirrmacher wrote on the front page of the «FAZ»[117] that «we are in the centre of a scientific-ethical revolution that affects not only societies and nations but the entire human species»[118].

Another media representative whose role extended beyond that of a simple mediator between the political actors and the public was Michael Naumann. The former Minister of State for Culture and then co-publisher as well as editor-in-chief of the weekly intellectual newspaper «Die Zeit», Naumann was, like Schirrmacher, and especially prior to the first stem cell legislation, a noted critic of embryonic stem cell research and therefore a representative of the «Und bloß kein Dammbruch»-concept. Naumann did not consider the National Ethics Council to be

[114] F. SCHIRRMACHER, *Privatschule des Lebens. Der Embryo im Zeitalter Gerhard Schröders*, in «FAZ», 22 May 2001, p. 49.

[115] *Ibidem.*

[116] *Ibidem.*

[117] Therapeutic cloning is one of the procedures used to obtain embryonic stem cells. Thereby therapeutic cloning serves for the production of blastocysts, from which stem cells can be procured.

[118] FRANK SCHIRRMACHER, *Die Evolution in unserer Hand*, in «FAZ», 21 December 2000, p. 1.

a good idea by Chancellor Schröder[119]. He said that the Council could be called a «pharmaceutical-industrial council for legitimizing»[120] the position of Chancellor Schröder. Moreover, Naumann claimed that an unambiguous judgement of the German Supreme Court, according to which developing life stands «from the outset» under the absolute protection of Article 1 Sec. 1 of the Constitution, was opposed to all experiments with human embryos[121].

As stated above, the decisions of the German Supreme Court concerning the beginning of the absolute protection enshrined in Article 1 Sec. 1 of the Constitution are definitely not as unambiguous as Naumann alleged. Hence his claim concerning the beginning of human dignity, as well as his criticism of the National Ethics Council, demonstrate his critical attitude towards stem cell research. This position became also apparent in the parallel that Naumann drew between Jürgen Habermas' «instrumentalized embryo»[122] of contemporary biotechnology and the nineteenth-century notion of the manipulated «biomass human being»[123]. Also in an article published in April 2002 during the week of voting on the first German stem cell law, Naumann expressed his «Und bloß kein Dammbruch»-stance: «The dams are breaching»[124]. The parliament had engaged in bioethical hair splitting in order to render homage to an economic progress which should transform into pharmaceutical profits[125]. Almost polemically, Naumann continued thus: The population is wiser. According to a survey, 71% of Germans reject the use of an embryo for «a medical or scientific purpose which does not serve the life of the embryo»[126]. Yet many delegates seemed to see the matter differently. Hence, Naumann contended, aside from a «genetic

[119] M. NAUMANN, *Biomasse Mensch. Der Embryo ist kein Ersatzteillager*, in «Die Zeit», 2001, 20, p. 1.

[120] *Ibidem.*

[121] *Ibidem.*

[122] *Ibidem.*

[123] *Ibidem.*

[124] M. NAUMANN, *Moralischer Hörsturz. Oder: Taube Kinder auf Bestellung*, in «Die Zeit», 2002, 18, p. 1.

[125] *Ibidem.*

[126] *Ibidem.*

deafness»[127] also a case of a «moral hearing loss»[128] seemed to exist[129]. This raises the question of how such thoughts expressed by Naumann as a media representative could be reconciled with his own expressed position that the privileged forum for political-ethical discourses was the parliament[130].

But even if Naumann charged the parliamentarians in favour of a liberal stem cell legislation with a «moral hearing loss», he was naturally of the opinion that any comparison of the serious ethical attempt to justify contemporary biogenetics with the racist justifications of the «Third Reich» would be abysmally wrong[131].

IV. Concluding remarks

In conclusion, I would point out that the decade-long German public stem cell debate – since Oliver Brüstle's application in 2000 – exhibited overall a growing liberalizing tendency. This feature stands out in spite of the deeply-rooted German historical experiences and ideas. It became evident in the parliamentary debates on the stem cell issue of 2002, 2007 and 2008, as well as in the corresponding hearings of the Subcommittee of Education, Research and Technology and the written statements by the scientific experts. Hence, the «Und bloß kein Dammbruch»-attitude was apparent not only in the content of the positions but also in how this debate was conducted in Germany. Apart from the constantly high quality of the contributions, also the willingness to compromise – especially in parliament – was remarkable. The extensive creation of the diverse councils and commissions proves that it was felt necessary to obtain broad consensus in society for regulation in such an important bioethical field. In particular, the councils and commissions contributed significantly to compromise-

[127] *Ibidem.*

[128] *Ibidem.*

[129] *Ibidem.*

[130] M. Naumann, *Biomasse Mensch*, p. 1.

[131] M. Naumann, *Der Staat und die Heiligkeit des Lebens. Bioethik ohne Gott ist möglich. Sie muss nur die Erfahrungen der deutschen Geschichte aufnehmen*, in «Die Zeit», 2001, 26, p. 4.

building within the German stem cell debate. Moreover, especially the Protestant Church in Germany played a pacifying role. And finally the extensive and engaged participation of the media – as a mediator between politicians and the public as well as an active participant in the process of political communication – made the German stem cell debate an example of successful political communication.

Legal Developments in Stem Cell Research in Germany

by *Jochen Taupitz**

I. The legal position under the Act of 28 June 2002

1. *Introduction*

It was in 2000 that the German researcher Oliver Brüstle officially applied for support from the Deutsche Forschungsgemeinschaft (DFG) (German Research Foundation, GRF) for a research program which required the importing into Germany of human embryonic stem cells from abroad[1]. This gave rise to heated debates on the ethical and legal acceptability of the importation of such stem cells, given that their production requires the «consumption» of embryos. While the Embryo Protection Act (EPA) of 13 December 1990, in force since 1 January 1991[2], prohibits such use of embryos in Germany, it does not include a provision regarding the importation of stem cells created by such means. This was considered by some as an implicit permission to import, by others as an unintentional loophole in the Embryo Protection Act.

The German Research Foundation was asked by political circles to delay its decision on Brüstle's request, so that the legislative body could have time to decide the matter. This request was granted by the GRF. Thereafter the GRF[3], as well as two newly-founded political advisory

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1 Brüstle had already given notice of his application some months earlier; therefore discussion on the importation of embryonic stem cells began before 2000.

2 *Bundesgesetzblatt* (Federal Law Gazette), I, 1990, 2746.

3 Deutsche Forschungsgemeinschaft (German Research Foundation), *Humane embryonale Stammzellen*, Stellungnahme vom 19. März 1999, in Senatskommission für

boards, gave their opinions. While the committee of inquiry Recht und Ethik der modernen Medizin (Law and Ethics of Modern Medicine), appointed by the German Bundestag on 24 March 2001, spoke out against the importing of embryonic stem cells[4], the majority of members of the Nationaler Ethikrat (National Ethics Council), set up on 2 May 2001 by the German Government, demanded a time-limited and strict ruling which would allow the importation of embryonic stem cells[5].

On 30 January 2002 the German Bundestag discussed three proposals with which a formal legislation procedure was to be initiated:

– The Proposal by the Members of Parliament Wodarg and others advocated, «with a view to protecting the dignity of embryos and in light of the Embryo Protection Act», a prohibition on the importation of embryonic stem cells without exception[6].

– The Proposal by the Members of Parliament Flach, Reiche, Hintze and others argued for importation to be made permissible as long as the embryonic stem cells came from leftover (supernumerary) embryos which had been donated for high-ranking scientific research. Moreover, after a scientific and ethical investigation, a commission should have allowed this importation[7].

– The Proposal by the Members of Parliament Böhmer, von Renesse, Fischer and others recommended legislation that prohibited the consumption of further embryos in order to obtain embryonic stem cells. The importation of stem cells was only to be allowed under tight restrictions and for scientific research[8].

The last Proposal received the majority of votes and formed the basis of the Stem Cell Act, which was passed on 28 June 2002.

GRUNDSATZFRAGEN DER GENFORSCHUNG (ed.), *Humangenomforschung – Perspektiven und Konsequenzen / Genome Research – Perspektive and Consequenzes*, 2000, pp. 3 ff.

4 Bundestag-Drucksache (printed matter of Parliament, hereafter BT-Drucks.) 14/7546.

5 NATIONALER ETHIKRAT, *Zum Import menschlicher embryonaler Stammzellen*, Berlin 2002. See with more details M. BREWE, *Embryonenschutz und Stammzellgesetz*, Berlin 2006, here pp. 54 ff.

6 BT-Drucks., 14/8101.

7 BT-Drucks., 14/8103.

8 BT-Drucks., 14/8102.

The Act, which ensures the protection of embryos in connection with the importation and use of human embryonic stem cells (Stem Cell Act, SCA / Gesetz zur Sicherstellung des Embryonenschutzes im Zusammenhang mit Einfuhr und Verwendung menschlicher embryonaler Stammzellen – Stammzellgesetz, StZG)[9], entered into force on 1 July 2002. It regulates the importation and use of human embryonic stem cells (hES cells).

The importation and the use of embryonic stem cells are in principle prohibited [s. 4 (1) in conjunction with s. 1 no. 2 SCA]. In particular circumstances, however, importation and use are exceptionally permissible [s. 4 (2) in conjunction with s. 1 no. 3 SCA]. According to s. 1 SCA, it is the purpose of the Stem Cell Act «in consideration of the State's obligation to respect and protect human dignity and the right to life and to guarantee the freedom of research ... 1. to prohibit, in principle, the importation and use of embryonic stem cells, 2. to prevent German demand from causing the derivation of embryonic stem cells or the production of embryos with the aim of deriving embryonic stem cells, and 3. to determine the requirements to exceptionally permit the importation and use of embryonic stem cells for research purposes only».

Stem cells, under s. 3 no. 1 SCA, are «all human cells which have the potential to multiply by cell division if in a suitable environment and which by themselves or through their daughter cells are capable, under favourable conditions, of developing into specialised cells, but not into a human being (pluripotent stem cells)».

Embryonic stem cells, under s. 3 no. 2 SCA, are «all pluripotent stem cells derived from embryos which have been extracorporeally produced and have not been used to bring about pregnancy or which have been taken from a woman before the completion of nidation».

In this connection, an embryo is «any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail» (s. 3 no. 4 SCA). It is irrelevant whether the totipotent cell has itself been taken from an embryo (unlike in s. 8 of the Embryo Protection Act).

[9] «Bundesgesetzblatt», I, 2002, pp. 2277-2280.

2. *Protection of living embryos abroad: Cutoff date provision (key date provision)*

The central concern of the Act is the provision which deals with from the derivation (= procurement) of stem cells from embryos and is aimed at the protection of living embryos abroad. Under s. 4 (2) no. 1 (a) SCA, embryonic stem cells may be imported and utilised, if at all, provided that «the competent agency has satisfied itself that ... the embryonic stem cells were derived before 1 January 2002[10] in the country of origin in accordance with relevant national legislation there and are kept in culture or are subsequently stored using cryopreservation methods (embryonic stem cell line)». This «cutoff date provision» or «key date provision» intends to prevent embryos available abroad from being utilised for the purposes of German research. In other words, the prohibition of an «instrumental use» of embryos according to s. 2 EPA is also applied to the derivation of embryonic stem cells abroad[11].

3. *Disapproval or prevention of particularly reprehensible acts in connection with the derivation of stem cells*

S. 4 (2) SCA contains further provisions concerning the derivation of hES cells. They are evidently based on the consideration that the derivation of stem cells may not be preceded by any act regarded as particularly reprehensible by the legislator[12]. They are therefore based on the ethical but constitutionally questionable[13] prohibition of «harvesting

[10] On the reform of the statute, see III below.

[11] Legislative rationale of the draft Stem Cell Act of 27 February 2002, BT-Drucks., 14/8394, p. 8; see also C. STARCK, *Embryonic Stem Cell Research according to German and European Law*, in «German Law Journal», 7, 2006, pp. 625-655, here, p. 641.

[12] J. TAUPITZ, *Erfahrungen mit dem Stammzellgesetz*, in «Juristenzeitung», 3, 2007, pp. 113-122.

[13] On the unconstitutionality of the restrictions of the Stem Cell Act extending beyond the cutoff date provision, see, in addition to the sources cited at note 25 below, Wolfrum, Schriftliche Stellungnahme of 7 March 2002, Drucks. 14-574 des Ausschusses für Bildung, Forschung und Technikfolgenabschätzung des Deutschen Bundestages (Committee on Education, Research and Technology Assessment of the German Bundestag); Löwer, Schriftliche Stellungnahme of 8 March 2002, Drucks. 14-574 I des Ausschusses für Bildung, Forschung und Technikfolgendabschätzung des Deutschen Bundestages (Committee on Education, Research and Technology Assessment of the

the fruit of a poisonous tree»[14]. The restrictions would only provide independent future-oriented protection for embryos (located abroad) if the cutoff date provision were repealed.

Under s. 4 (2) no. 1 (b) SCA, it must be demonstrated to the satisfaction of the authorising agency that the embryos from which the stem cells have been derived were created by means of medically assisted extracorporeal fertilisation for the purpose of effecting a pregnancy. This excludes, inter alia, the importation and use of hES cells which come from embryos created by means of cell nuclear transfer («therapeutic cloning», «Dolly» method), because this method does not consist of «fertilisation». The requirement of extracorporeal fertilisation prevents the importation of stem cells obtained from embryos which have been created by means of an intracorporeal fertilisation process (insemination or gamete intrafallopian transfer) and then again removed from the mother before nidation by means of uterine lavage, at the mother's wish. In addition, the stem cells must come from embryos created for the purpose of bringing about a pregnancy, without ultimately being used for this purpose (known as supernumerary embryos). In any case, these embryos had no chance of survival. By contrast, not permissible are the importation and use of stem cells from embryos created for the purpose of deriving stem cells or for the purpose of research. Moreover, the decision to reject the embryos must not have been taken for reasons to do with the embryos themselves. As a consequence, the importation and use of stem cells from embryos rejected on the basis of pre-implantation diagnosis (PID) are not permissible. Finally, no payment or any non-cash benefit is allowed to be granted or promised in return for the permission to use the embryos to derive stem cells [s. 4 (2) no. 1 c) SCA]. Thus, on the one hand, commercialisation is avoided, while on the other, it is also ensured that the decision of the genetic parents to permit use of the embryo for research has not been made in a situation of financial distress.

German Bundestag); J. TAUPITZ, *Alternativlosigkeit als Voraussetzung der Forschung mit embryonalen Stammzellen*, in *Jahrbuch für Wissenschaft und Ethik*, Berlin 2003, pp. 341 ff., with further references; in addition see below section II.5.

[14] J. TAUPITZ, *Erfahrungen mit dem Stammzellgesetz*; dissenting: R. RÖGER, *Hochrangigkeit, Alternativlosigkeit und ethische Vertretbarkeit der Forschung an humanen embryonalen Stammzellen aus verfassungsrechtlicher Sicht*, in «Jahrbuch für Wissenschaft und Ethik», Berlin 2003, pp. 322 ff.

4. *Protection of other provisions of German law*

S. 4 (2) SCA contains a third group of requirements, which protect other prohibitions within German law: there may be no other statutory provisions, in particular those of the Embryo Protection Act [s. 4 (2) no. 2 SCA], which prevent the importation and use of hES cells[15]. In addition, approval must be refused if the derivation of the stem cells occurred in manifest contradiction to fundamental principles of the German legal system [s. 4 (3) sentence 1 SCA][16]. However, the refusal of approval may expressly not be justified with the argument that the stem cells were derived from human embryos [s. 4 (3) sentence 2 SCA]. Since hES cells are by definition derived from human embryos, this provision serves to harmonise the Stem Cell Act with s. 2 EPA (prohibition on the use of embryos for purposes other than to effect a pregnancy). This shows that the legislator does not regard the (past) use of embryos for purposes other than to effect a pregnancy as one of the particularly reprehensible acts mentioned under I.3; that is, it does not regard the use of embryos to derive stem cells as being in itself a violation of human dignity[17].

5. *Restrictions on research work using embryonic stem cells in Germany*

The importation and the use of embryonic stem cells may be approved only for research purposes [s. 4 (2) SCA], and only if «the requirements of s. 5 SCA have been complied with and the research project is ethically justifiable in this sense» [s. 6 (4) no. 2 SCA][18].

S. 5 SCA has two partial requirements. Firstly, under s. 5 no. 1 SCA research work on embryonic stem cells may only be conducted «if it has been shown by giving scientific reasons that such research serves eminent research aims to gain scientific knowledge in basic research or

[15] For a more detailed treatment, see M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 194-195.

[16] For a more detailed treatment, see *ibidem*, pp. 195 ff.

[17] This is also the interpretation of H.-G. DEDERER, *Verfassungskonkretisierung im Verfassungsneuland – das Stammzellgesetz*, in «Juristenzeitung», 58, 2003, pp. 986-994.

[18] On this see C. HONECKER, *Was heißt «ethisch vertretbar»?*, in *Jahrbuch für Wissenschaft und Ethik*, Berlin 2003, pp. 361 ff.

to extend diagnostic, preventive or therapeutic methods to be applied to humans».

This criterion of eminence primarily relates to the aims of the intended research[19].

Secondly, under s. 5 no. 2 SCA it must have been shown with scientific reasons that «according to the state of the art of science and technology

a) the questions to be studied in the research project concerned have been clarified as far as possible through *in vitro* models using animal cells or in animal experiments and

b) the scientific knowledge to be gained from the research project concerned can only be expected to be achieved by using embryonic stem cells».

This second criterion concerns the means employed for this purpose. On the one hand, there must be sufficient prior clarification that the research project intends to answer the involved questions with experiments on animals or animal cells (so that it is «now» necessary to continue research with human cells). On the other hand, it must be shown that the knowledge to be gained cannot be achieved in any other way than by research using human embryonic stem cells (for example by research using adult cells or cells from umbilical cord blood).

Both partial requirements may be reduced to the (linked) aspects of necessity and subsidiarity, which can be summarised in the expression «lack of alternatives»[20].

The provisions described above do not, therefore, refer in a past-oriented manner to the circumstances of the creation, which took place abroad. Instead, in a future-oriented manner, they provide the additional requirements which are to be complied with in Germany. These provisions, which also restrict research, apply – as does the whole Stem Cell Act – (only) to stem cells, that is, to cells that as such are not

[19] On this in more detail, see M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 199 ff.; H.-G. DEDERER, *Hochrangigkeit von Zielen der Stammzellforschung im Lichte des Grundgesetzes*, in *Jahrbuch für Wissenschaft und Ethik*, Berlin 2003, pp. 305 ff.; R. RÖGER, *Hochrangigkeit,* pp. 314 ff.

[20] In more detail on this, M. BREWE, *Embryonenschutz und Stammzellgesetz*, here pp. 199 ff.; R. RÖGER, *Hochrangigkeit*; J. TAUPITZ, *Alternativlosigkeit als Voraussetzung*, pp. 335 ff.; J. TAUPITZ, *Der Schutz embryonaler Stammzellen durch das Stammzellgesetz*, in «GenTechnik & Recht», 2003, pp. 12 ff.

totipotent and therefore are generally held not to enjoy any protection of human dignity and life[21]. In the opinion of the legislator, the research restrictions which are nevertheless laid down in the Act are justified by the fact that embryonic stem cells may not «from the ethical point of view» be regarded in the same way as every other form of human material, since in order to derive them it has been necessary to destroy embryos[22]. The «fruit of the poisonous tree» is therefore not to be used at will; its use indeed is to be «reduced to a minimum»[23]. But ethical misgivings as such cannot justify a restriction of the freedom of research guaranteed by the constitution[24]. Nor does the doctrine of the fruit of the poisonous tree, which is of great importance in the ethics debate, have a place in a constitutional discussion about possible restrictions of the freedom of research. In the opinion of other writers[25], however, the restrictions of the Stem Cell Act create a «post-mortem protection of the human dignity of prenatal life»[26]. But this view is not convincing either. Admittedly, the Federal Constitutional Court has in fact recognised post-mortem protection of human dignity as such in several decisions[27],

[21] H.-G. DEDERER, *Hochrangigkeit von Zielen der Stammzellforschung*, p. 307; J. RAASCH, *Das Stammzellgesetz – ein beladenes Gesetzesvorhaben*, in «Kritische Justiz», 35, 2002, p. 294; J. TAUPITZ, *Import embryonaler Stammzellen. Konsequenzen des Bundestagsbeschlusses vom 31-1-2001*, in «Zeitschrift für Rechtspolitik», 2002, p. 113.

[22] BT-Drucks., 14/8394, p. 7.

[23] BT-Drucks., 14/8394, p. 9.

[24] But yielding a difficult outcome, BT-Drucks. 16/7983, p. 2 (on this, see section III below).

[25] M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 109 ff. with further references; rejecting this, H.-G. DEDERER, *Hochrangigkeit von Zielen der Stammzellforschung*, pp. 308-309; K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung an humanen pluripotenten embryonalen Stammzellen und ihre Würdigung im Stammzellgesetz*, Berlin 2006, pp. 83 f.; J. TAUPITZ, *Der Schutz embryonaler Stammzellen.*

[26] The expression is taken from Löwer, written opinion of 8 March 2002, Drucks. 14-574 l des Ausschusses für Bildung, Forschung und Technikfolgendabschätzung des Deutschen Bundestages (Committee on Education, Research and Technology Assessment of the German Bundestag); Löwer himself speaks of «constitutionally absolutely unsecured terrain».

[27] Decisions of the Federal Constitutional Court (Entscheidungen des Bundesverfassungsgerichts - BVerfG) 30, p. 194; «Neue Juristische Wochenschrift», 1994, p. 784; «Neue Juristische Wochenschrift», 2001, p. 594; «Neue Juristische Wochenschrift», 2001, pp. 2958-2959.

but this protection is linked to the fact that each person in question lived and worked in the human community («among us»). In essence, therefore, this protection concerns the memory of someone who was part of a social community. This idea, however, cannot be transferred to embryos *in vitro*.

In addition, a state's legal system is not responsible for the protection of legal interests situated abroad in the same way as it is for those within the country[28]. This shows a fundamental difference between law and morality: whereas morality and ethics are universally oriented, law (apart from international law) is based on the idea of state sovereignty. This does not exclude protection of universal legal interests. In addition, states are required to punish the violation of legal interests which are recognised in all civilised states, irrespective of the territory and the nationality of the perpetrator (universality principle). International law, too, is based on the principle of worldwide application. But the global legal community (*Weltrechtsgemeinschaft*) has no common understanding of the appropriate protection of embryos *in vitro*, as the diversity of provisions shows[29]. For this reason, if embryos are destroyed abroad without any relation to Germany, this does not make it mandatory that the use of the stem cells derived from the embryos should subsequently be subject to restrictive conditions in Germany. Against the background of these arguments, a considerable number of authors regard the restrictions of the Stem Cell Act which exceed the cutoff date provision as unconstitutional[30].

[28] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, Berlin 2007, pp. 40 f.; M. KLOEPFER, *Humangentechnik als Verfassungsfrage*, in «Juristenzeitung», 57, 2002, pp. 417-428, here p. 426; K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung*, pp. 81 ff.; R. MÜLLER-TERPITZ, *Die neuen Empfehlungen der DFG zur Forschung mit menschlichen Stammzellen*, in «Wissenschaftrecht: Wissenschaftsverwaltung, Wissenschaftsförderung», 34, 2001, pp. 279-280; J. TAUPITZ, *Der «ethische Export» als Rechtsproblem biomedizinischer Forschung, dargestellt aus dem Blickwinkel des deutschen Rechts*, in Th. GEISER et al. (eds), *Festschrift für Heinz Hausheer. Privatrecht im Spannungsfeld zwischen gesellschaftlichem Wandel und ethischer Verantwortung*, Bern 2002, pp. 740 ff.; for a more restrictive view see M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 98 ff.; R. RÖGER, *Hochrangigkeit*, pp. 314-318 ff.

[29] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, p. 40.

[30] Evidence above fn 13; see also the critical voices cited above in fn 25.

6. *No legalisation of the past destruction of embryos*

In none of the above provisions does the Stem Cell Act pronounce that the derivation of embryonic stem cells abroad is legal. Nor does the Stem Cell Act place eminent research above the protection of the life of embryos. Instead, the Act merely permits the importation and use of stem cells which were derived in the past, which means that the utilisation of the ensuing embryos occurred in the past and cannot be reversed. As long as the importation and use is permitted of those stem cells which were derived in compliance with the legal position in the country of origin [s. 4 (2) no. 1 a) SCA], it is to be particularly emphasised that the question as to whether and subject to what requirements destructive embryo research is permitted or prohibited abroad is to not be judged by German law, but by the relevant foreign law[31].

The attitude of the legislator in rejecting the derivation of stem cells, on the one hand, but authorising the importation and use of embryonic stem cells on the other (albeit subject to very strict requirements), is unobjectionable from a constitutional point of view (I. 5 above). However, this is criticised as «morally lazy» or as an expression of «double moral standards»[32]. It is claimed that it is «absolutely unacceptable» to leave foreign researchers to carry out the derivation of embryonic stem cells which is rejected in Germany, while at the same time making use of the results. In this regard, it is not uncommon (but questionable)[33]

[31] BT-Drucks., 14/8846, p. 13; with constitutional objections to this provision M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 167 ff.

[32] See in detail R. MERKEL, *Forschungsobjekt Embryo, Verfassungsrechtliche und ethische Grundlagen der Forschung an menschlichen embryonalen Stammzellen*, München 2002, pp. 217 ff.; BIOETHIK-KOMMISSION DES LANDES RHEINLAND-PFALZ, *Bericht Medizinische, ethische und juristische Bewertung der Forschung an humanen embryonalen Stammzellen unter Einbeziehung des Stammzellgesetzes vom 28. Juni 2002*, 23 August 2002, p. 52; J. RAASCH, *Das Stammzellgesetz – ein beladenes Gesetzesvorhaben*, pp. 294-295; U. SCHROTH, *Forschung mit embryonalen Stammzellen und Präimplantationsdiagnostik im Lichte des Rechts*, in «Juristenzeitung», 57, 2002, p. 178.

[33] See NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, pp. 18-19: The need to sanction the receiving of stolen goods usually follows from the mere fact that it has a causal effect on the perpetuation of robbery and theft, which cannot normally be assumed of the use of stem cells produced abroad. Besides, receiving stolen goods requires prior criminal acts which are without doubt ethically and legally condemned everywhere; but this is decidedly not the case with regard to the production of embryonic stem cells, since this is permitted in many countries.

for a parallel to be drawn with receiving stolen goods. Others point out that it is arbitrary to lay down a fixed date from which the doctrine of the fruit of the poisonous tree henceforth applies; one should either always take the position that it is wrong to eat the fruit of the poisonous tree, or one should reject this principle[34]. However, moral objections to the use of the fruit of past wrong do not *per se* exclude any weighing of interests whatsoever. They may be subordinated if the use serves eminent interests and goals, for example the treatment of serious illnesses[35]. Thus, assisted reproduction, which is now firmly established in Germany, was and is based on knowledge arising from destructive embryo research undertaken in other countries[36]. Quite generally, it is certainly necessary to distinguish between an act that produces something and an act that merely uses the product[37].

In addition, there is the following problem. Not even the strict German Embryo Protection Act prohibits the destruction of embryos as such. When embryos – for whatever reason – cannot be transferred to a woman for the purpose of reproduction, there is no requirement to preserve them. It is therefore undisputed that there is no obligation to keep them alive; they may be disposed of[38]. It is to be doubted whether the disposal constitutes a violation of human dignity solely because the embryos are not merely «disposed of», but additionally used to derive stem cells. This can hardly be regarded as a «scornful disparagement» according to the judicature of the Federal Constitutional Court. This applies independently of the controversial question as to whether embryos *in vitro* should be seen as deserving the protection of human dignity at all (and if so, with what intensity). The Stem Cell Act, in turn, permits at most the importation and use of stem cells from such embryos which – because they could not be transferred to a woman – had no

[34] U. SCHROTH, *Forschung mit embryonalen Stammzellen und Präimplantationsdiagnostik im Lichte des Rechts*, in F.S. ODUNCU - U. SCHROTH - W. VOSSENKUHL (eds), *Stammzellenforschung und therapeutisches Klonen*, Göttingen 2002, p. 280.

[35] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, p. 19.

[36] *Ibidem.*

[37] J. TAUPITZ, *Erfahrungen mit dem Stammzellgesetz*, p. 118.

[38] J. TAUPITZ, in H.-L. GÜNTHER - J. TAUPITZ - P.T. KAISER, *Embryonenschutzgesetz: Juristischer Kommentar mit medizinisch-naturwissenschaftlicher Einführung*, Stuttgart 2008, § 1, Abs. 1, Nr. 3, margin note 7.

real chance of life. Since, therefore, even the original act of using the embryo does not constitute an obviously serious injustice, it must all the more be doubted whether the act of exploitation, that is, the use of embryonic stem cells, can be disapproved of in itself.

It may, however, be established that the Act, against the background of starkly diverging views, has at least made an important contribution to social pacification which has existed for quite some time[39].

7. *Procedural protection*

Two institutions are competent to review the above material requirements: every importation and every use of embryonic stem cells must be approved by the Robert Koch-Institute[40]. Its approval depends not only on the above-named requirements of s. 4 (2) SCA; in addition, there must also be an opinion given by the Central Ethics Commission for Stem Cell Research (Zentrale Ethikkommission für Stammzellforschung), whose members are representatives of biology, ethics, medicine and theology. The Central Ethics Commission for Stem Cell Research, for its part, must (only) determine whether or not the requirements of s. 5 SCA (eminent research with no alternatives) are satisfied and the research project is, in this sense, ethically justifiable[41].

II. Reform discussion and suggested legislation prior to the Bundestag decision of 11 April 2008

1. *Cutoff date provision*

The much-discussed original cutoff date (1 January 2002) was set earlier than the date when the Act came into force (1 July 2002). The intention

[39] S. Roesler, *Das deutsche Stammzellgesetz – Spezifische Fragen der Auslegung des Gesetzes*, in «Jahrbuch für Wissenschaft und Ethik», 8, 2003, p. 283.

[40] This follows from s. 6 SCA in conjunction with the delegated legislation supplementing the Stem Cell Act.

[41] On the scope of the Commission's powers of review, see M. Brewe, *Embryonenschutz und Stammzellgesetz*, pp. 224 ff.; J. Taupitz, *Die Aufgaben der Zentralen Ethikkommission für Stammzellforschung*, in K. Amelung et al. (eds), *Strafrecht – Biorecht – Rechtsphilosophie. Festschrift für Hans-Ludwig Schreiber*, Heidelberg 2003, pp. 903 ff.

was to prevent destruction of embryos «on orders» originating from Germany[42]. But by establishing a fixed cutoff date in the past (as in the case of the new cutoff date – on this, see III below), the legislator went too far back. It did so in order to also exclude acts that are only distantly or not at all responsible for causing the destruction of embryos. There is no concrete legal attribution of a particular causal element. Consequently, a researcher cannot prove that no embryo was destroyed specifically as a result of him/her ordering the stem cells. Instead, the Act is based on the general suspicion that every destruction of embryos in order to derive embryonic stem cells after the cutoff date has been ordered from Germany if these stem cells are then used for German research.

The constitutionality of the cutoff date provision is and was the subject of intense discussion. The opinion has been expressed that the cutoff date provision is necessary for the purpose of the greatest possible protection of life[43]. In addition, it is claimed that there are no objections to it with regard to the prerogative of assessment and drafting which the Federal Constitutional Court grants to the legislature. According to this opinion, adapting the cutoff date to a later date («flexible cutoff date») would not achieve the legislator's aim in an equally suitable manner.

However, this opinion is not convincing. The cutoff date provision, within the system of the legislation (prohibition subject to approval), is an exception to the prohibition of importation and use, but at the same time it *de facto* prohibits the importation and use of all embryonic stem cells produced after the cutoff date. As said above, this is intended to prevent (indirectly, that is, by preventing sale to Germany) a (further) destruction of embryos being brought about from Germany. But this is already directly guaranteed by the Embryo Protection Act in conjunction with the provisions of international criminal law [s. 3

[42] ZENTRALE ETHIKKOMMISSION BEI DER BUNDESÄRZTEKAMMER, *Stellungnahme zur Stammzellforschung* vom 19. Juni 2002 (Opinion on stem cell research of 19 June 2002 of the Central Ethics Commission at the German Medical Association), printed in J. TAUPITZ, *Rechtliche Regelung der Embryonenforschung im internationalen Vergleich*, Berlin - Heidelberg 2003, p. 269. See also the legislative rationale on the draft Stem Cell Act of 27 February 2002, BT-Drucks., 14/8394, p. 9.

[43] K. FASSBENDER, Der *Schutz des Embryos und die Humangenetik: Zur Verfassungsmäßigkeit des neuen Stammzellgesetzes und des Embryonenschutzgesetzes im Lichte des einschlägigen Arzthaftungsrechts*, in «Medizinrecht», 21, 2003, p. 283.

to 7, 9 of the German Criminal Code (*Strafgesetzbuch - StGB*)]. This provides that every participation of German researchers from Germany in stem cell derivation abroad is prohibited and a criminal offence, even if the act is not a criminal offence in its location[44]. All that the cutoff date provision in the Stem Cell Act and the associated prohibition of importation and use do is to additionally cover cases in which foreign researchers or enterprises produce hES cells on their own initiative, but motivated by the expectation of later demand from Germany, and with the intention of then exporting them to Germany. However, this case is somewhat far from reality. There is a global demand for embryonic stem cells. In addition, the existing cell lines can be kept in culture for a very long time and can be propagated at will. Thus it cannot be assumed that additional embryos are destroyed or have to be destroyed specifically to satisfy the need for stem cells in Germany[45]. Altogether, therefore, a connection between the number of embryonic stem cells used in Germany and the number of embryos destroyed abroad is extremely questionable[46]. In other words, the Stem Cell Act causes great detriment to research in Germany, without in turn creating a protection of foreign embryos which extends beyond the Embryo Protection Act[47]. In constitutional terms, this means that the prohibition of importation and use of the Stem Cell Act in conjunction with the

[44] S. 5 no. 12 *StGB* contains even stricter provisions for German public officials. This also applies in particular to members of universities, but also to members of quasi-governmental non-university institutions. Cf. A. ESER - H.G. KOCH, *Forschung mit humanen embryonalen Stammzellen im In- und Ausland. Rechtsgutachten*, in DEUTSCHE FORSCHUNGSGEMEINSCHAFT (ed.), *Forschung mit humanen embryonalen Stammzellen. Strafrechtliche Grundlagen und Grenzen*, Weinheim 2003, pp. 151 ff.

[45] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, pp. 16, 41 f.; ZENTRALE ETHIKKOMMISSION BEI DER BUNDESÄRZTEKAMMER, *Stellungnahme zur Stammzellforschung* vom 19. Juni 2002, p. 269; Opinion of DEUTSCHE FORSCHUNGSGEMEINSCHAFT, *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, 2006 (downloadable at http://www.dfg.de/aktuelles_presse/themen_dokumentationen/stammzellen/dfg_publikationen_stammzelforschung.html), p. 60; also K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung*, pp. 85-86.

[46] Cf. C.D. CLASSEN, *Die Forschung mit embryonalen Stammzellen im Spiegel der Grundrechte*, in «Deutsches Verwaltungsblatt», 117, 2002, p. 147.

[47] «The German legislator, in prohibiting the importation of embryonic stem cells, does not in principle ... make a genuine contribution to the protection of embryos», *ibidem*, p. 147.

cutoff date provision entails a disproportionate encroachment upon the freedom of research[48].

The situation has been aggravated by the fact that the effects of the cutoff date provision were increasingly tending towards the complete prohibition of research before the revision of the Stem Cell Act in 2008:

– This results from the fact that the «old» hES cells, which were derived before the original cutoff date (1 January 2002), were of a considerably inferior quality. Unlike the «new» hES cells, they were cultivated on layers of animal cells and thus could not be used therapeutically because of a serious risk of infection should they be used on human beings. For this reason, the research work that has been approved may have to be repeated with other stem cells, either later or at another location, because the characteristics of the cells complying with the old cutoff date provision may differ from those of the cells later used in the clinic[49].The interest of German enterprises in investing in stem cell research has consequently been very limited.

– The stem cell lines produced before 1 January 2002 were not isolated and cultivated under standardised conditions pursuant to the rules of good laboratory practice or good manufacturing practice. Further, suboptimal culturing conditions in part resulted in genetic and epigenetic changes. The expression patterns and development stages of the stem cell lines produced before 1 January 2002 are therefore very heterogeneous. This too had a detrimental effect on their suitability for basic research, and all the more so for later clinical and therapeutical use on humans.

– The importation of hES cells produced abroad before 1 January 2002 makes researchers in Germany dependent on foreign patents and licences. Detailed material transfer agreements usually make sure that the research results obtained with the imported cell lines are (co-) owned by the producers. In addition, there is an obligation to disclose unpublished data to the producing enterprise as well. Now, there are

[48] Thus also stated by U. SCHROTH, *Forschung mit embryonalen Stammzellen*, p. 280; K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung*, pp. 85 ff.; see also F. HUFEN, *Erosion der Menschenwürde?*, in «Juristenzeitung», 59, 2004, p. 318.

[49] See the fears of this of the ZENTRALE ETHIKKOMMISSION FÜR STAMMZELLFORSCHUNG (Central Ethics Commission for Stem Cell Research), *Dritter Bericht* of 14 December 2005 (downloadable at http://www.rki.de/cln_011/nn_228928/DE/Content/Gesund/Stammzellen/ZES/ Taetigkeitsberichte/taetigkeitbericht-inhalt.html), p. 6.

a number of new cell lines which have been made freely available to science, so that they can be used without accepting these restrictions. However, German researchers could not use these freely available cell lines, because they were not produced before 1 January 2002. So the cutoff date provision very substantially strengthened foreign monopolies. Another result was that the authoritative standards were laid down abroad. But above all, German enterprises were discouraged from investing in stem cell research. This was because later commercial applications were normally covered by the foreign patent, and there could therefore be hardly any expectation of profit in Germany. The lack of commercial prospects, in turn, had negative effects on the development of basic research itself.

– The cutoff date provision resulted in considerable problems in international cooperations, because there was an extremely high risk that criminal offences would be committed by German and foreign researchers in collaborative projects where the work involved the use of «new» stem cell lines. Consequently, German researchers were hardly ever involved in international cooperations, and found it very difficult to persuade foreign researchers to cooperate on joint projects. The problem of the increasing international isolation of German researchers was emphasised by large number of opinions and reports: for example, those by the Central Ethics Commission at the German Medical Association[50], the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften)[51], the Central Ethics Commission for Stem Cell Research[52], the Bio-Ethics Commission of the *Land* Rhineland-Palatinate (Bioethik-Kommission des Landes Rheinland-Pfalz)[53], the GRF[54] and the German National

[50] ZENTRALE ETHIKKOMMISSION BEI DER BUNDESÄRZTEKAMMER, *Stellungnahme zur Stammzellforschung* of 19 June 2002, p. 270.

[51] Opinion of 11 July 2003 of the ARBEITSGEMEINSCHAFT DER WISSENSCHAFTLICHEN MEDIZINISCHEN FACHGESELLSCHAFTEN (Association of the Scientific Medical Societies in Germany) (downloadable at http://www.uni-duesseldorf.de/www/awmf/res/res-estz.htm).

[52] ZENTRALE ETHIKKOMMISSION FÜR STAMMZELLFORSCHUNG, *Dritter Bericht*, p. 6.

[53] BIOETHIKKOMMISSION RHEINLAND-PFALZ, report *Fortpflanzungsmedizin und Embryonenschutz* of 12 December 2005, pp. 71-72, 115.

[54] DEUTSCHE FORSCHUNGSGEMEINSCHAFT, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, pp. 5 ff., 52 ff.

Ethics Council[55]. The German Bundestag also considered this problem as early as in 2005[56]. Admittedly, at that time the cutoff date provision was probably the only political possibility of continuing with at least a small part of basic research. In fact, over time it has resulted in a nearly complete prohibition of research with hES cells in Germany[57]. This consequence is constitutionally more than questionable: the constitutional mandate to protect embryos situated abroad is indisputably unlike that of embryos situated in Germany[58]. Moreover, it is the declared goal of the Stem Cell Act itself not to prevent stem cell research in Germany entirely; but the effect, created by the Act itself, is an equivalent to a prohibition which is inconsistent with the declared goal.

From the point of view of legal policy too, the cutoff date came under increasing pressure as it became clear that German researchers were excluded from international progress. Thus, for example, the FDP parliamentary group in the German Bundestag as early as in 2005[59] and the German Research Foundation in 2006[60] called for the cutoff date to be abolished, while the literature also called for a «flexible» cutoff date[61]. In 2007, the German National Ethics Council suggested that the cutoff date should be replaced, and instead that each case should be considered individually in order to judge whether or not the derivation of stem cells has been initiated from Germany[62].

[55] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, pp. 31 ff.

[56] Minor interpellation of the FDP parliamentary group of 15 March 2005 on the cooperation of German scientists with foreign scientists in EU stem cell research projects, BT-Drucks. 15/5165; answer of the Federal Government of 30 March 2005, BT-Drucks. 15/5196.

[57] For this case, however, the legislator's solution was described as unconstitutional immediately after the provision entered into effect: M. KLOEPFER, *Humangentechnik als Verfassungsfrage*, p. 427; J. RAASCH, *Das Stammzellgesetz – ein beladenes Gesetzesvorhaben*, p. 294.

[58] See above at fn 28.

[59] Motion of the FDP parliamentary group of 18 January 2005, BT-Drucks. 16/383; motion of the FDP parliamentary group of 1 June 2005, BT-Drucks. 15/5584.

[60] DEUTSCHE FORSCHUNGSGEMEINSCHAFT, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, pp. 7, 50-51.

[61] J. TAUPITZ, *Erfahrungen mit dem Stammzellgesetz*, pp. 117 f.

[62] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, p. 51.

2. *Risks of criminal liability in international collaborative research*

A serious problem with the original Stem Cell Act was – as mentioned above – the possible criminal liability of German and foreign researchers if they were involved in an international collaboration (for example in the Sixth or Seventh EU Framework Programme).

S. 13 (1) SCA read as follows: «Any person who imports or uses embryonic stem cells without approval pursuant to s. 6 (1) shall be liable to imprisonment of up to three years or to a fine». It was disputed whether «use» only means «use within Germany» or whether the general system of criminal law on liability for involvement in acts abroad also applied, so that a researcher who collaborated from within Germany with another researcher legally carrying out stem cell research abroad was also criminally liable.

Admittedly the literature increasingly and correctly maintained that the area of application of the Stem Cell Act was restricted from the outset to German territory, since only importing into Germany and use in Germany could be approved[63]. Following this opinion, however – contrary to the discussions in the course of deliberation on the Act[64] – *participation* (instigating or aiding and abetting) in the use of embryonic stem cells abroad was not punishable under s. 13 SCA in conjunction with s. 9 (2) German Criminal Code. For if the principal offence in which the instigator or accessory participates can, by reason of the restricted territorial application of the Stem Cell Act, only be committed in Germany, then participating in an act abroad cannot be a criminal offence.

However, the uncertainty remained as to whether this interpretation of the Stem Cell Act – which was certainly not undisputed[65] – would also be

[63] A. ESER - H.G. KOCH, *Rechtsgutachten*, pp. 118 ff.; H. DAHS - B. MÜSSIG, *Forschung mit humanen embryonalen Stammzellen im In- und Ausland. Rechtsgutachten*, in DEUTSCHE FORSCHUNGSGEMEINSCHAFT (ed.), *Forschung mit humanen embryonalen Stammzellen*, pp. 18 ff.; M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 250 ff.

[64] For a more detailed treatment, see M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 251-252.

[65] A different view is advanced by, e.g., E. HILGENDORF, *Strafbarkeitsrisiken bei der Stammzellforschung mit Auslandskontakten*, in «Zeitschrift für Rechtspolitik», 39, 2006, pp. 23 f.

shared by the courts. In addition, even according to this opinion, there remained the risk of criminal liability for joint commission and indirect commission. This is because under the general system of criminal law, an accomplice in Germany is also held liable for his or her contribution to an act which is committed abroad[66]. This risk existed in particular in the case of close collaboration where work was shared with a person researching abroad (legally under the foreign law). Consequently, a German researcher committed an offence under the German Stem Cell Act if the foreign researcher with whom s/he was collaborating worked with embryonic stem cells abroad, even if that foreign researcher worked in accordance with the local law. The international exchange of scientists also carried a particular risk of criminal liability under s. 5 no. 12 or no. 13 German Criminal Code if they were «officials» or «persons with particular obligations for the civil service»[67]. If German criminal law was to be interpreted broadly, in some circumstances even foreign researchers, working with stem cells abroad, committed criminal offences under the German Stem Cell Law (!)[68].

All this gave rise to considerable uncertainty among German and foreign scientists; and as a result the international competitiveness of German researches and their ability to collaborate was increasingly called into question (II.1 above). In its opinion of November 2006, the GRF pointed out that it knew of examples of scientists who had deliberately avoided this area of research, or had withdrawn from it, because of what they thought was a lack of prospects and because embryonic stem cell research was frequently discredited in Germany[69]. The Opinion stated that this was not only reflected in the relatively small number of applications made, but also in the global comparison of the number of publications on the subject: German researchers were virtually unrepresented.

It was widely argued that legal certainty would be attained if it were made clear both in s. 2 SCA and in s. 13 SCA that the Stem Cell Act

[66] A. Eser - H.G. Koch, *Rechtsgutachten*, pp. 136 ff.; E. Hilgendorf, *Strafbarkeitsrisiken bei der Stammzellforschung*, p. 24.

[67] See in more detail A. Eser - H.G. Koch, *Rechtsgutachten*, pp. 151 ff.

[68] E. Hilgendorf, *Strafbarkeitsrisiken bei der Stammzellforschung*, p. 24.

[69] Deutsche Forschungsgemeinschaft, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, p. 54.

relates only to the use of stem cells located in Germany[70]. In addition, the German National Ethics Council called for the provision of s. 13 SCA, which created a criminal offence, to be downgraded into a provision creating a regulatory offence[71]. The demands of the GRF went even further[72]: it called for s. 13 SCA to be completely discarded.

3. *The restriction of the use of stem cells to research purposes*

The prohibition of the use of hES cells for every purpose except narrowly-defined research forbids their use for diagnostic, therapeutic and preventive purposes, although stem cell research is above all intended to serve the purpose of developing new therapies. This prohibition also applies to individual attempts to achieve a cure, which normally precede clinical trials (which themselves constitute research)[73], and all the more so precede the use of tested therapies in clinical practice. The restriction of the importation of stem cells for research purposes was and is therefore criticised as short-sighted and inconsistent[74]. There are calls to permit the use of human embryonic stem cells for health-related purposes as well. Failing this, German research – as the Central Ethics Commission for Stem Cell Research complained – will remain restricted «to creating fundamental principles for the future use of the cells for therapeutic, preventive and diagnostic purposes outside Germany»[75]. But also this contribution to research will increasingly atrophy, because

[70] NATIONALER ETHIKRAT, *Zur Frage einer Änderung des Stammzellgesetzes*, pp. 47-48.

[71] *Ibidem*, pp. 48-49, 51-52.

[72] DEUTSCHE FORSCHUNGSGEMEINSCHAFT, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, pp. 8, 61-62.

[73] Clinical trials are permissible under the SCA; as also argued in R. MÜLLER-TERPITZ, *Humane Stammzellen und Stammzellderivate*, in «Jahrbuch für Wissenschaft und Ethik», 2006, pp. 90 f.

[74] BIOETHIK-KOMMISSION DES LANDES RHEINLAND-PFALZ, report *Fortpflanzungsmedizin*, pp. 75 f., 115; ZENTRALE ETHIKKOMMISSION FÜR STAMMZELLFORSCHUNG, *Dritter Bericht*, pp. 4 ff.; DEUTSCHE FORSCHUNGSGEMEINSCHAFT, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, pp. 7, 61 f.; M. BREWE, *Embryonenschutz und Stammzellgesetz*, pp. 198 f.; K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung*, here pp. 89-90; J. RAASCH, *Das Stammzellgesetz*, p. 293; U. SCHROTH, *Forschung mit embryonalen Stammzellen*, p. 280; J. TAUPITZ, *Import embryonaler Stammzellen*, p. 104.

[75] ZENTRALE ETHIKKOMMISSION FÜR STAMMZELLFORSCHUNG, *Dritter Bericht*, p. 6.

the Stem Cell Act prevents the indispensable cooperation of scientific research and clinic application[76].

However, an extension of the legitimate uses is problematical because it can scarcely be implemented while the current requirement of official approval of every «use» continues to be in effect. It is therefore understandable that the discussions in parliament (III below) have excluded this point.

4. *The prohibition of the importation of stem cells from intracorporeally fertilised embryos*

Under s. 4 (2) no. 1 b) SCA, imported stem cells may not have been derived from intracorporeally fertilised embryos (I.3 above). No plausible justification can be seen for prohibiting the use of such embryos for the derivation of stem cells, provided that the other requirements of the Stem Cell Act are fulfilled[77]. Nor is it furnished in the legislator's statement of intention. The literature therefore calls for this restriction to be removed[78].

5. *The prohibition of the importation of stem cells from embryos that were not created by means of fertilisation*

HES cells make it possible to analyse the development processes of diseases on the cellular level by establishing cell lines from embryos that carry genetic defects which cause specific diseases. These cells also make it possible to test new medicinal products *in vitro* before they are used on human beings. New hES cell lines established since the cutoff date are now available for the investigation of thalassemia, Huntington's disease, muscular dystrophy and other genetic disorders[79]. They were either created by the method of cell nuclear transfer or derived from embryos which were not transferred to the mother as the result of a

[76] K. KLOPFER, *Verfassungsrechtliche Probleme der Forschung*, p. 90.

[77] J. RAASCH, *Das Stammzellgesetz*, p. 294.

[78] J. TAUPITZ, *Erfahrungen mit dem Stammzellgesetz*, p. 120.

[79] DEUTSCHE FORSCHUNGSGEMEINSCHAFT, opinion *Stammzellforschung – Möglichkeiten und Perspektiven in Deutschland*, pp. 34 f.

PID. However, s. 4 (2) no. 1 b) SCA provides that such cells may not be imported into Germany (I.3 above). As a result, research using these disease-specific hES cells is prohibited in Germany. And yet, precisely such research would be desirable, not least in pharmacogenetics or toxicity testing, because it avoids endangerment to patients. Here too there are calls in the literature for the relaxation of the statute's restrictions[80], but there has been no activity in parliament to date.

III. Parliamentary initiatives resulting in the decision of the German Bundestag of 11 April 2008

In the spring of 2008, five bills were introduced to the German Bundestag proposing an amendment to the Stem Cell Act. The bills reflected the entire spectrum of opinions in Germany on the question of the permissibility of research with embryonic stem cells. The most radical proposal[81] called for both the cutoff date provision and the criminal provision of the Act to be repealed without replacement. But this would not have corresponded to the logic of the Act (although it would have been constitutional). The less radical second proposal[82] provided for the cutoff date to be changed to 1 May 2007; further, it also restricted the area of application of the Act as a whole and also of the criminal provision expressly (in addition to importation) to embryonic stem cells situated «in Germany». This was intended to counteract the considerable legal uncertainties in regard to the risk of criminal liability in international cooperations arising from the previous version of the Act (II.2 above). The third bill[83] envisaged the same restriction to embryonic stem cells situated in Germany, but it did not alter the cutoff date. A fourth proposal[84], by contrast, called for the existing legal position to remain unchanged and for the promotion of research using

[80] J. Taupitz, *Erfahrungen mit dem Stammzellgesetz*, pp. 120 f.

[81] *Entwurf eines Gesetzes für eine menschenfreundliche Medizin – Gesetz zur Änderung des Stammzellgesetzes*, BT-Drucks., 16/7982 (new).

[82] *Entwurf eines Gesetzes zur Änderung des Stammzellgesetzes*, BT-Drucks., 16/7981.

[83] *Entwurf eines Gesetzes zur Änderung des Stammzellgesetzes*, BT-Drucks., 16/7984.

[84] Motion for a decision entitled *Keine Änderung des Stichtages im Stammzellgesetz – Adulte Stammzellforschung fördern*, BT-Drucks., 16/7985.

adult stem cells. Finally, a fifth proposal[85] urged a complete prohibition of the importation and use of embryonic stem cells, because research with them was unnecessary and no therapeutic uses could be foreseen.

On 11 April 2008, the German Bundestag, after intense discussion, voted in favour of the second proposal (Bundestag printed paper 16/7981), by a clear majority of 346 votes to 228, with 6 abstentions[86]. As a result, the cutoff date was moved to 1 May 2007 and the area of application of the Act as a whole and also of the criminal provision was expressly restricted to the importation of embryonic stem cells and the use of embryonic stem cells situated «in Germany».

The alteration of the cutoff date was entirely in compliance with the basic intention of the Stem Cell Act (I.2 above). It was also compliant with the view, also rightly expressed in the Stem Cell Act, that acts of exploitation must be evaluated differently from acts of production, and that (assumed) injustice in the past is not undone or eliminated by prohibition of the act of exploitation. In addition, the original Act already contained the possibility of an amendment to the Act by changing the cutoff date. The duty to provide information, which was and is imposed on the Federal Government by s. 15 SCA[87], can have no purpose other than permitting the experience gained in implementation of the Act to be incorporated, where appropriate, in discussions on an amendment of the Act. Otherwise, the requisite report would not need to be provided to the German Bundestag, which has sole responsibility for the amendment of the Act.

However, it is not very convincing that a cutoff date relatively far in the past (1 May 2007) was chosen; this holds true regarding the date

[85] *Entwurf eines Gesetzes zur Änderung des Gesetzes zur Sicherstellung des Embryonenschutzes im Zusammenhang mit menschlichen embryonalen Stammzellen*, BT-Drucks., 16/7983.

[86] Second and third reading, *Bundestagsprotokolle* (Minutes of Bundestag Plenary Proceedings) 16/155; the first reading of the bills took place on 14 February, *Bundestagsprotokolle* 16/142. In its session 844 of 23 May 2008, the Bundesrat rejected the motion of Bavaria of 20 May 2008 (Bundesrat Drucks., 278/08) for an appeal to the Mediation Committee (Vermittlungsausschuss).

[87] «The Federal Government shall submit to the Deutscher Bundestag a report presenting the experience gained with the implementation of the present Act every two years, beginning the end of 2003. The report shall also describe the results of research using other types of human stem cells».

when the amendment to the Act was passed (11 April 2008), as well as the date when it entered into effect (21 August 2008)[88]. The date of 1 May 2007 was clearly chosen because there was a hearing in the Committee on Education, Research and Technology Assessment of the German Bundestag on 9 May 2007[89] and this was obviously regarded as the signal for the discussions in parliament on an amendment of the Stem Cell Act to start. However, it cannot seriously be assumed that, in the following months, even one single stem cell line was produced abroad because there was a discussion in Germany in May 2007 on an amendment to the Stem Cell Act, with the possibility of the cutoff date being changed or removed as a consequence. Firstly, it should be obvious to every foreign researcher that a discussion – on an extremely controversial issue – in a committee of the German Bundestag does not automatically result in a statute. And secondly, the significance of the German market (as shown by the small number of research projects carried out there to date) is not likely to be so great that it gives notable impetus to the production of embryonic stem cell lines abroad. It must therefore again be emphasised that the unconstitutionality is all the more tangible the further the cutoff date lies in the past, even if it is in fact moved, yet on the date when the amendment to the Act enters into effect, it is still a considerable time in the past.

The clarification concerning the application of the Act and its criminal provision, that is, the specific restriction of the prohibition on use of hES cells to those located in Germany is more than welcome. The full implications of the uncertainties in relation to the risk of criminal liability (II.1 above) were clearly not fully understood when the Act was passed. In addition, it can also be assumed that this was not desired at the time and that «use» was to be interpreted as use in Germany. The amendments therefore correspond to the fundamental intention of the Stem Cell Act: to deal with the importation of stem cells and also with their use in Germany.

[88] The Act was promulgated in the «Bundesgesetzblatt» (Federal Law Gazette) on 20 August 2008 and pursuant to its Article 2 it therefore entered into effect on 21 August 2008.

[89] Protokoll 16/53 des Ausschusses für Bildung, Forschung und Technikfolgenabschätzung des Deutschen Bundestages (Minutes 16/53 of the Committee on Education, Research and Technology Assessment of the German Bundestag).

IV. Final remarks

1. In the discussions in parliament, there was and is clearly agreement that the Embryo Protection Act is not to be touched. This means that the production of embryonic stem cells will continue to remain prohibited in Germany.

2. The political discussion on the law regulating embryonic stem cell research will continue in Germany. In the near future, it will above all be the turn of the scientists to speak. It will be their research results that determine whether research using human embryonic stem cells will continue to be seen as necessary, whether it must even be expanded, or whether, on the contrary, it will become obsolete, so that retrospectively it is seen that Germany made the right decision in taking an extremely restrictive position compared with that of other countries.

3. The Stem Cell Act relates to a rather small area of biomedical research. However, it clearly has a symbolic significance which extends far beyond its concrete area of application. This is the only explanation for the heated discussion, sometimes accompanied by a great deal of emotion, that it generated. However, it is inappropriate to stir up fears in the population with the argument that the destruction of embryos will soon be followed by the killing of humans already born, for example old people and sick people, for the purposes of research. Such an argument ignores the ability of a society to differentiate – and the responsibility of parliament as the legislator. Significantly, the liberalisation of the abortion law did not lead to a weakening of the right to life of human beings already born. This also applies to the permissibility of the abortion of defective embryos and foetuses. On the contrary: the sensitisation of society for the needs of people with disabilities has increased, possibly even because embryos and foetuses in the womb do not have an absolute right to life.

Appendix: The German Law

Act ensuring protection of embryos in connection with the importation and utilization of human embryonic stem cells
– Stem Cell Act –
(*Stammzellgesetz – StZG*) of 14 August 2008
(unofficial translation)

The Bundestag has adopted the following Act:

Section 1
Purpose of the Act

In consideration of the State's obligation to respect and protect human dignity and the right to life and to guarantee the freedom of research, the purpose of the present Act is

1. to ban, as a matter of principle, the importation and utilization of embryonic stem cells,
2. to prevent demand in Germany from causing the derivation of embryonic stem cells or the production of embryos with the aim of deriving embryonic stem cells, and
3. to determine the requirements for permitting, as an exception, the importation and utilization of embryonic stem cells for research purposes.

Section 2
Scope

The present Act shall apply to the importation of embryonic stem cells and the utilization of embryonic stem cells which are located in Germany.

Section 3
Definitions

For the purpose of the present Act

1. stem cells mean all human cells which have the potential to multiply by cell division if in a suitable environment and which by themselves or through their daughter cells are capable, under favourable

conditions, of developing into specialized cells, not, however, into a human being (pluripotent stem cells),

2. embryonic stem cells mean all pluripotent stem cells derived from embryos which have been produced in vitro and have not been used to induce pregnancy or which have been taken from a woman before completion of nidation,
3. embryonic stem cell lines mean all embryonic stem cells which are kept in culture or those which are subsequently stored using cryopreservation methods,
4. embryo means any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail,
5. importation means the introduction of embryonic stem cells into the territorial scope of the present Act.

SECTION 4

Importation and utilization of embryonic stem cells

(1) The importation and utilization of embryonic stem cells shall be prohibited.

(2) Notwithstanding para 1, the importation and utilization of embryonic stem cells for research purposes shall be permissible under the conditions stipulated in section 6 if

1. the competent agency has satisfied itself that

a) the embryonic stem cells were derived before 1 May 2007 in the country of origin in accordance with relevant national legislation there and are kept in culture or are subsequently stored using cryopreservation methods (embryonic stem cell line),

b) the embryos from which they were derived have been produced by medically-assisted in vitro fertilization in order to induce pregnancy and were definitely no longer used for this purpose and that there is no evidence that this was due to reasons inherent in the embryos themselves,

c) no compensation or other benefit in money's worth has been granted or promised for the donation of embryos for the purpose of stem cell derivation and if 2. other legal provisions, in particular those of the German Embryo Protection Act , do not conflict with the importation or utilization of embryonic stem cells.

(3) Approval shall be refused if the embryonic stem cells have obviously been derived in contradiction to major principles of the German legal system. Approval may not be refused by arguing that the stem cells have been derived from human embryos.

SECTION 5
Research using embryonic stem cells

Research involving embryonic stem cells shall not be conducted unless it has been shown by giving scientific reasons that

1. such research serves eminent research aims to generate scientific knowledge in basic research or to increase medical knowledge for the development of diagnostic, preventive or therapeutic methods to be applied to humans and that,
2. according to the state-of-the-art of science and technology,
   a) the questions to be studied in the research project concerned have been clarified as far as possible through in vitro models using animal cells or through animal experiments and
   b) the scientific knowledge to be obtained from the research project concerned cannot be expected to be gained by using cells other than embryonic stem cells.

SECTION 6
Approval

(1) Any importation and any utilization of embryonic stem cells shall be subject to approval by the competent agency.
(2) Applications for approval must be submitted in writing. In the documents accompanying the application, the applicant shall provide the following information in particular:
   1. Name and official address of the person responsible for the research project concerned,
   2. a description of the research project including scientific reasons showing that the research project meets the requirements set forth in section 5 above,
   3. a documentation concerning the embryonic stem cells to be imported or used showing that the requirements set forth in no. 1 of para 2 of section 4 above have been complied with or equivalent evidence that

a) the embryonic stem cells to be imported or used are identical with those registered in a scientifically recognized, publicly accessible registry maintained by government agencies or agencies authorized by the government and that,
b) by way of such registration, the requirements set forth in no. 1 of para 2 of section 4 above have been complied with.

(3) The competent agency shall immediately acknowledge in writing receipt of the application and the attached documents. At the same time, the agency shall request the opinion of the Central Ethics Commission on Stem Cell Research. On receipt of the opinion, the agency shall notify the applicant of the content and the date of the opinion adopted by the Central Ethics Commission on Stem Cell Research.

(4) Approval shall be given if
1. the requirements set forth in para 2 of section 4 above have been complied with,
2. the requirements set forth in section 5 above have been complied with and, accordingly, the research project is ethically acceptable, and if
3. an opinion by the Central Ethics Commission on Stem Cell Research has been submitted following a request by the competent agency to this effect.

(5) If the application, complete with documentation, and the opinion of the Central Ethics Commission on Stem Cell Research have been received, the agency shall decide in writing on the application within a period of two months. In doing so, the agency shall consider the opinion adopted by the Central Ethics Commission on Stem Cell Research. If the competent agency's decision differs from the opinion adopted by the Central Ethics Commission on Stem Cell Research, the agency shall give its reasons in writing.

(6) Approval can be limited in time or by imposing obligations to the extent necessary for complying with or continuing to meet the approval requirements pursuant to para 4 above. If, following approval, events occur which conflict with the granting of approval, approval can be withdrawn wholly or in part with effect in the future or be limited in time or be made dependent on the fulfilment of conditions to the extent necessary for complying with or continuing to meet the approval requirements set forth in para 4

above. Any objection to or action for rescission of withdrawal or revocation of approval shall not suspend the effect of the decision.

SECTION 7
Competent agency

(1) The Federal Ministry for Health shall determine by ordinance which authority in its portfolio shall be the competent agency. The agency shall discharge – as federal administrative tasks – the duties assigned to it by virtue of the present Act and shall be supervised by the Federal Ministry for Health.
(2) Costs (fees and expenses) shall be charged for official acts performed by virtue of the present Act. The law on administrative costs shall apply. In addition to the exemption of the legal entities mentioned in para 1 of section 8 of the law on administrative costs, non-profit research organizations shall be exempt from paying any fees.
(3) The Federal Ministry for Health shall be authorized to determine, by ordinance and in agreement with the Federal Ministry of Education and Research, the acts which shall be subject to a fee, providing for fixed rates or tiered rates. In fixing such rates, the importance, the commercial value or any other benefit arising from approval for those having to pay fees shall be taken into account.

The ordinance can provide for a fee to be charged for an uncompleted official act if the person who requested the official act is responsible for noncompletion.

(4) The applicants' own expenses incurred in the course of providing the information the agency requires to decide on approval shall not be reimbursed.

SECTION 8
The Central Ethics Commission on Stem Cell Research

(1) An independent, interdisciplinary Central Ethics Commission on Stem Cell Research shall be established at the competent agency; it shall be composed of nine experts from the disciplines of biology, ethics, medicine and theology.

The experts to be nominated shall include four members from the disciplines of ethics and theology and five scientists from the fields of biology and medicine.

The Commission shall elect a chair and a deputy chair from among its members.

(2) The members of the Central Ethics Commission on Stem Cell Research shall be appointed by the Federal Government for a three years' term. Reappointment is possible. As a rule, a deputy shall be appointed for each member.

(3) The members and their deputies shall be independent and not bound by instructions. They shall be obliged to observe secrecy. Sections 20 and 21 of the Law on Administrative Procedures shall apply mutatis mutandis.

(4) The Federal Government shall be authorized to enact an ordinance specifying the details concerning the appointment of, and the procedure to be followed by, the Central Ethics Commission on Stem Cell Research, the invitation of external experts, and cooperation with the competent agency including deadlines.

SECTION 9

Duties of the Central Ethics Commission on Stem Cell Research

The Central Ethics Commission on Stem Cell Research shall examine and evaluate applications and accompanying documents in order to determine whether the requirements set forth in section 5 above have been complied with and, accordingly, the research project is ethically acceptable.

SECTION 10

Confidentiality

(1) The application documents referred to in section 6 above shall be treated as confidential.

(2) Notwithstanding para 1 above, the following data may be entered into the registry referred to in section 11 below:

1. the information to be provided on the embryonic stem cells in accordance with no. 1 of para 2 of section 4 above,
2. the name and official address of the person responsible for the research project,
3. basic data concerning the research project, in particular a brief description of the planned research specifying the reasons for its eminence, naming the institution where the research will be conducted and indicating its expected duration.

(3) If an application is withdrawn before a decision on approval has been made, the competent agency shall delete the data stored in connection with the application and return such application and accompanying documents.

SECTION 11
Registry

Information on the embryonic stem cells and basic data concerning approved research projects shall be registered by the competent agency in a publicly accessible registry.

SECTION 12
Obligation to notify

The person responsible for the research project has to notify the competent agency without delay of any major changes occurring after application which affect the permissibility of the importation or utilization of the embryonic stem cells in question.
Section 6 shall remain unaffected.

SECTION 13
Penal provisions

(1) Any person who
1. imports embryonic stem cells or
2. uses embryonic stem cells which are located in Germany

without having obtained approval pursuant to para 1 of section 6 above shall be punished with imprisonment of up to three years or shall be fined. Any person who obtains approval by deliberately giving false information shall be deemed to have acted without approval within the meaning of the preceding sentence. The attempt shall be punishable.

(2) Any person who fails to meet a binding requirement imposed pursuant to the first or second sentence of para 6 of section 6 above shall be punished with imprisonment of up to one year or shall be fined.

SECTION 14
Provisions on administrative fines

(1) An administrative offence shall be deemed to be committed by any person who,
   1. contrary to the second sentence of para 2 of section 6 above, provides incorrect or incomplete information or,
   2. contrary to the first sentence of section 12 above, does not notify changes or gives an incorrect, incomplete or belated notification.

(2) The administrative offence can be punished with an administrative fine of up to fifty thousand Euro.

SECTION 15
Report

The Federal Government shall submit to the Deutscher Bundestag a report presenting the experience gained with the implementation of the present Act every two years, beginning at the end of 2003. The report shall also describe the results of research using other types of human stem cells.

SECTION 16
Entry into force

The present Act shall enter into force on the first day of the month following promulgation.

Stem Cell Research in Germany with Specific Regard to Human Embryonic Stem Cells

by *Anna M. Wobus** and *Peter Löser***

I. Historical reflections

Research on pluripotent stem cells dates back to the middle of the last century, when Leroy Stevens discovered the relationship between early embryos and the formation of teratocarcinomas, these being transplantable tumours containing embryonic carcinoma (EC) cells – the stem cells of malignant teratocarcinomas[1]. *In vitro* cultivation and characterization of EC cells revealed self-renewal and differentiation as properties characteristic of stem cells[2].

Research on EC cells in those early days – summarized at the Cold Spring Harbor Conference on «Teratocarcinoma Stem Cells» in September 1982 – marked the advent of pluripotent stem cell research[3]. Although it became evident that EC cells developed chromosomal aberrations resulting in a lack of pluripotency after integration into mouse embryos,

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1 L.C. Stevens, *The Development of Transplantable Teratocarcinomas from Intratesticular Grafts of Pre- and Postimplantation Mouse Embryos*, in «Developmental Biology», 21, 1970, pp. 364-382.

2 See A.M. Wobus - K.R. Boheler, *Embryonic Stem Cells: Prospects for Developmental Biology and Cell Therapy*, in «Physiological Reviews», 85, 2005, pp. 635-678; A.M. Wobus, *The Janus Face of Pluripotent Stem Cells – Connection between Pluripotency and Tumourigenicity*, in «BioEssays», 32, 2010, pp. 993-1002.

3 L.M. Silver - G.R. Martin - S. Strickland (eds), *Teratocarcinoma stem cells* (Cold Spring Harbor Conferences on Cell Proliferation, 10), Cold Spring Harbor NY 1983.

this research provided the basis for later studies involving embryonic stem cells (ESCs): In 1981, based on their work with *in vitro* cultivated mouse EC cells, Martin Evans and Matthew Kaufman, as well as Gail Martin, independently established «true» pluripotent ESCs by directly cultivating mouse embryos that circumvented the tumourigenic stage of teratocarcinomas[4]. In the following years, various groups, mainly in the UK and the United States, worked with murine ESCs. In Germany, two groups established mouse ESC lines and characterized the cells by *in vitro* differentiation, teratocarcinoma formation and karyotype analyses[5].

Research on mouse ESCs during the 1980s and early 1990s concentrated on characterization of their properties, the optimization of *in vitro* propagation, differentiation into derivatives of all three germ layers, and development of strategies for genetic modification by gain-of-function and loss-of-function (gene targeting)[6]. But only the derivation of the first human embryonic stem cell (hESC) lines by James Thomson and co-workers at the end of 1998[7] attracted significant public attention. The prospect of generating specialized human cells from an unlimited cell source raised hopes of therapies for hitherto incurable human diseases. However, a fundamental drawback of hESC derivation, the necessity to destroy early human embryos at the blastocyst stage, raised ethical concerns and heavily affected the public debate on the use of hESCs.

To be pointed out is that research on embryonic stem cells developed independently of the discovery of adult hematopoietic stem cells by James Till and Ernest McCulloch in the early 1960s, when hematopoi-

[4] M.J. Evans - M.H. Kaufman, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, in «Nature» 291, 1981, pp. 154-156.; G. Martin, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, in «Proceedings of the National Academy of Sciences», 78, 1981, pp. 7634-7638.

[5] A.M. Wobus - H. Holzhausen - P. Jäkel - J. Schöneich, *Characterization of a Pluripotent Stem Cell Line Derived from a Mouse Embryo*, in «Experimental Cell Research», 152, 1984, pp. 212-219.; T.C. Doetschman et al., *The in vitro Development of Blastocyst-derived Embryonic Stem Cell Lines: Formation of Visceral Yolk Sac, Blood Islands and Myocardium*, in «Journal of Embryology & Experimental Morphology», 87, 1985, pp. 27-45.

[6] A.M. Wobus - K.R. Boheler, *Embryonic Stem Cells.*

[7] J.A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, in «Science», 282, 1998, pp. 1145-1147.

etic stem cells were characterized as multipotent stem cells capable of self-renewal and differentiation[8]. Thus, contrary to claims by opponents of hESC research, embryonic stem cell research is not a mere product of progress in adult stem cell research; rather, it has different roots.

II. Stem cell research in Germany within the Priority Program 1109 of the German Research Foundation 2001-2007

Germany was among those countries in which the derivation of the first hESC lines in 1998 rapidly caused heated debate on stem cell research. Scientists, scientific organisations, and the public discussed the potential and challenges, but also the ethical and possible legal implications, of hESC research. In spring 1999, the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) began its first consultations on stem cell research with cell biologists, stem cell researchers and physicians. The aim of this initiative was to induce synergistic effects by concentrating different stem cell research activities into a specific research program. A series of meetings followed with the purpose of establishing a Priority Program (*Schwerpunktprogramm*) for stem cell research. In March 2000, a first project proposal *Embryonic and tissue-specific stem cells – Regenerative systems for cell and tissue repair* was submitted, and in June 2000 the Senate of the DFG recommended the funding of a Priority Program with the following areas prioritized for project applications: (1) genetics and cell biology of the asymmetric division of somatic stem cells including model organisms; (2) analysis of the developmental capacity of (mouse) ESCs and integration of differentiated cell types into animal models; (3) analysis of somatic stem cells with emphasis on stem cell plasticity; and (4) germ cells and mechanisms of reprogramming. To be noted is that the use of hESCs and the legal situation of working with hESCs were at that time still under discussion in Germany. In January 2001, the funding of the first 16 projects of the DFG Priority Program 1109 started, and in the following years a total of 26 projects were supported in 2- or 3-year funding periods between 2001 and 2007[9].

[8] J.E. Till - E.A. McCulloch, *A Direct Measurement of the Radiation Sensitivity of Normal Mouse Bone Marrow Cells*, in «Radiation Research», 14, 1961, pp. 213-222.

[9] A.M. Wobus, *Stem Cell Research within the Priority Program 1109 of the German Research Foundation, 2001-2007*, in «Cells Tissues Organs», 188, 2008, pp. 6-8.

III. Human ESC research in Germany according to the Stem Cell Act

In 1999, the DFG issued a first statement on research involving hESCs, followed by a second statement on *Research with Human Embryonic Stem Cells* presented to the public in May 2001. In parallel, this topic was discussed by the German Federal Parliament's Commission of Inquiry into *Prospects and Risks of Modern Medicine* and by a newly established National Ethics Council, which submitted a joint report at the end of 2001. After a first parliamentary debate in December 2001, the Federal Government implemented the parliamentary resolution in January 2002. The legislative process resulted in the Stem Cell Act (Stammzellgesetz, StZG), which became effective on 1 July 2002. The Embryo Protection Act, which prohibits the use of human embryos for research purposes, remained in force, with the consequence that the establishment of hESCs is prohibited in Germany.

The Stem Cell Act prohibits the import and use of hESCs as a basic principle, but at the same time defines circumstances under which hESCs may be imported into Germany and used for research purposes. The following requirements must be fulfilled with respect to the hESC lines in order to obtain a license for the import and use of hESCs: (1) the embryonic stem cells must have been derived before 1 January 2002 in the country of origin in accordance with its relevant national legislation there; (2) the embryos from which they were derived have been produced by medically assisted *in vitro* fertilisation to induce pregnancy and were definitely no longer used for this purpose, and that there is no evidence that this was due to reasons inherent to the embryos themselves; (3) no compensation or other payment in kind has been granted or promised for the donation of embryos for stem cell derivation.

Furthermore, the Stem Cell Act also defines the prerequisites that must be met by the research project in which the use of hESC lines is envisaged: (1) the research project must serve goals of a premium value for the acquisition of scientific knowledge; (2) results from appropriate preliminary experiments involving animal or non-ES human cells must exist to provide pre-clarification of the research project; and (3) the intended advance in scientific knowledge must require the use of hESCs and cannot be obtained by using a different cell type.

One rationale for these restrictions was to prevent research projects undertaken in Germany from causing further embryo destruction outside Germany.

The Central Ethics Commission (Zentrale Ethik-Kommission für Stammzellenforschung, ZES) is charged with the task of reviewing and evaluating research projects involving hESCs submitted by German scientists to the licensing authority, the Robert Koch Institute (RKI). The ZES must determine whether the research proposals comply with the regulations set forth in the Stem Cell Act, and it must submit a written opinion to the RKI. The first license for the import and use of hESCs was granted to Oliver Brüstle, of the University of Bonn, in December 2002. The project immediately became part of the DFG-funded Stem Cell Priority Program.

However, the Stem Cell Act had several shortcomings, two of which became apparent soon after its enforcement. First, from 1998 onwards, important advances were achieved in the hESC field, for example with respect to the derivation and cultivation of hESCs. The number of newly established hESCs continually increased, and derivation techniques steadily improved. Because of the cut-off date originally defined in the Stem Cell Act (1 January 2002), German researchers were initially allowed to work with only 21 hESC lines listed in the registry of the National Institutes of Health (NIH) of the United States. These hESC lines were not standardized and, in addition, they were potentially contaminated by animal cells and proteins. In fact, the so-called NIH hESC lines were established under non-standardized conditions in the presence of animal sera and supplements and cultured on animal feeder cells.

Consequently, German hESC research became increasingly restricted, and international cooperations proved difficult owing to the availability of only a few hESC lines in Germany. Second, it was not entirely clear from the wording of the Stem Cell Act whether a German researcher working abroad with hESCs or participating in international projects would be in breach of the Stem Cell Act. Consequently, it could not be excluded that German researchers would be confronted with legal problems in Germany as a consequence of international collaborations. Therefore, the German Research Foundation and the German academies (Berlin-Brandenburg Academy of Sciences; German Academy of Natural Sciences Leopoldina) independently published statements

on human ESC research and proposed an amendment to the Stem Cell Act. Specifically, a more recent cut-off date for the import and use of newly established hESC lines and the abandonment of penalties for violation of the Stem Cell Act have been recommended. After hearings and a parliamentary discussion, the amendments to the Stem Cell Act were adopted by the parliament and enacted in August 2008. According to the amended Stem Cell Act, a new cut-off date (1 May 2007) was set for the import of hESC lines. Moreover, the regulations concerning the area of application of the Stem Cell Act were modified so that it became unambiguously clear that only hESC research performed within Germany was subject to the regulations. However, the request of the DFG and the Academy of Leopoldina to allow the use of hESCs not only for research purposes but also for commercial and routine applications was not granted.

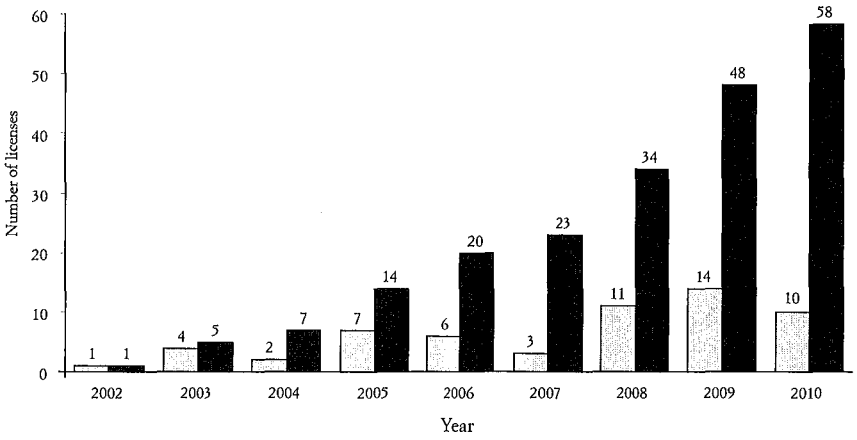
IV. The present state of hESC research in Germany

According to the Stem Cell Act, scientists who intend to work with hESCs in Germany must apply for a license. For each application, the Central Ethics Committee (ZES) examines whether the research proposal is in accordance with the regulations set forth by the Stem Cell Act. After review by the ZES, an opinion is submitted to the licensing authority (RKI), which must make the final decision on the application. Although the RKI is not constrained by the ZES's opinion, in the past there has been agreement between RKI and ZES on all applications. To date (December 2010), a total of 58 licenses for import and/or use of hESCs have been granted in Germany (see figure 1), while two proposals have been rejected and two projects have been discontinued.

At present, hESC research is being performed in 32 German institutions by 44 research groups. While many hESC projects are undertaken at universities and in the research groups of scientific organizations such as the Max-Planck-, Fraunhofer- and Helmholtz-Societies, some hESC research is also conducted by companies and scientific agencies (see table 1).

The geographical distribution of the institutions performing hESC research licensed by the RKI demonstrates that North-Rhine Westphalia with 20 projects occupies the leading position in German hESC research.

Figure 1. *Licences for import and/or use of hESCs*



Number of Licences for import and/or use of hESCs granted by the Robert Koch Institute (RKI) after approval by the Central Ethics Committee for Stem Cell Research (ZES) in the given years (light grey bars) and in total by the end of each year (dark grey bars). Two applications have been rejected both by ZES and the RKI to date. Four applications were pending at the end of 2010.

Source: Robert Koch Institute, www.rki.de

This may be due to the constant support given to stem cell research by the North-Rhine Westphalian government. Moreover, Berlin and Lower Saxony are regions in which several groups and institutions are engaged in research with hESCs, while other federal states play only a minor role (see fig. 2).

After the successful reprogramming of somatic cells to human-induced pluripotent stem cells (hiPSCs) by Shinya Yamanaka[10] and others[11] and after the amendments to the Stem Cell Act (see above), researchers in Germany broadened their research activities. Projects in which hESCs and hiPSCs were compared in regard to their characteristics and dif-

[10] K. Takahashi - S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defines Factors*, in «Cell», 126, 2006, pp. 663-676; K. Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, in «Cell», 131, 2007, pp. 861-872.

[11] J. Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, in «Science», 318, 2007, pp. 1917-1920.

Table 1. *German institutions using hESCs for research*

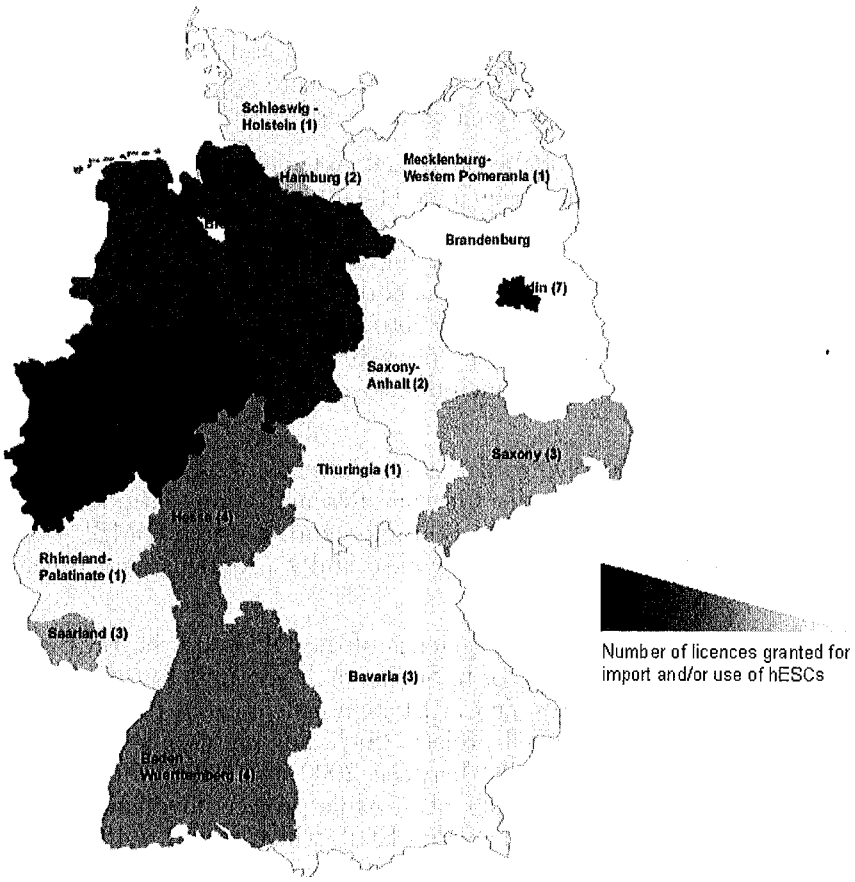
Institution	Number of Research Groups	Number of Licences
Research Organizations		
Max Planck Society	3	7
Fraunhofer Society	2	3*
Helmholtz Society (MDC Berlin)	3	3
Universities		
22 Universities and Medical Schools (Berlin, Bonn, Köln, Dortmund, Dresden, Düsseldorf, Essen, Frankfurt, Freiburg, Giessen, Göttingen, Halle, Hamburg, Hannover, Heidelberg, Jena, Konstanz, München, Münster, Rostock, Tübingen, Würzburg)	31	40
Companies		
ProteoSys AG (Mainz)	1	1
Miltenyi Biotec GmbH (Bergisch-Gladbach)	1	1
Life & Brain GmbH (Bonn)	1	1
(Private) Non-Profit Organizations		
ZIP gGmbH (Kiel)	1	1
Governmental Agencies		
Paul Ehrlich Institute (Langen)	1	1
Total: 32 Institutions	44	58

The number of groups working with hESCs at these institutions and the number of licenses granted by the Robert Koch Institute until the end of 2010 are shown.

* One research project was completed in December 2010.

Source: Robert Koch Institute, www.rki.de

Figure 2. *Regional distribution of projects involving hESCs among the federal states of Germany*



Shown is the number of projects approved by the Robert Koch Institute (RKI) by the end of 2010. All projects also received approval from the Central Ethics Committee for Stem Cell Research (ZES).

Source: Robert Koch Institute, www.rki.de

ferentiation properties were initiated, and newly established cell lines were imported into Germany for use in research projects. As shown in Figure 3, from 2007 onwards, research projects in which only hESCs were used and projects involving both hESCs and hiPSCs were initiated. Moreover, hESC lines derived between the old and new cut-off dates (between 1 January 2002 and 1 May 2007) were approved for import to Germany and for use in research projects (see table 2).

Before the amendment of the Stem Cell Act, only 20 hESC lines derived before the original cut-off date (1 January 2002) were approved by the licensing authority for import and use. Strikingly, in only two years after the amendment of the Stem Cell Act, licenses were granted for the import and use of an additional 23 hESC lines derived between 1 January 2002 and 1 May 2007. This reflects the strong interest of researchers in using these «new» hESC lines, and confirms the necessity to implement the much-discussed modifications to the Stem Cell Act.

Research projects involving hESCs in Germany were (and still are) financially supported by the German Research Foundation (DFG, table 3), the Federal Ministry of Education and Research (BMBF, table 4), the European Union in framework 6 and 7 programs, and private donors.

When considering the funding practice of the DFG and the BMBF, to be noted is that the funding of hESC research accounts for only a low percentage of the total funding of all stem cell research projects. The DFG supported all stem cell projects (including embryonic and adult human and animal stem cells) between 2000 and 2009, with a total amount of at least 93,89 million EUR, while projects involving hESCs received funding of only 5,11 million EUR, which is only 5.4% of the total amount spent for research on all stem cell types (see table 3).

At present, the DFG is supporting a number of ambitious stem cell programs. After the Priority Program 1109 was completed in 2007, the new stem cell Priority Program 1356 on *Pluripotency and Reprogramming* was begun. This program was launched in response to the breakthrough reprogramming studies by Shinya Yamanaka[12]. It funds

[12] K. TAKAHASHI - S. YAMANAKA, *Induction of Pluripotent Stem Cells*; K. TAKAHASHI et al., *Induction of Pluripotent Stem Cells.*

Table 2. *hESC lines approved for import to Germany and for use in research projects by the end of 2010*

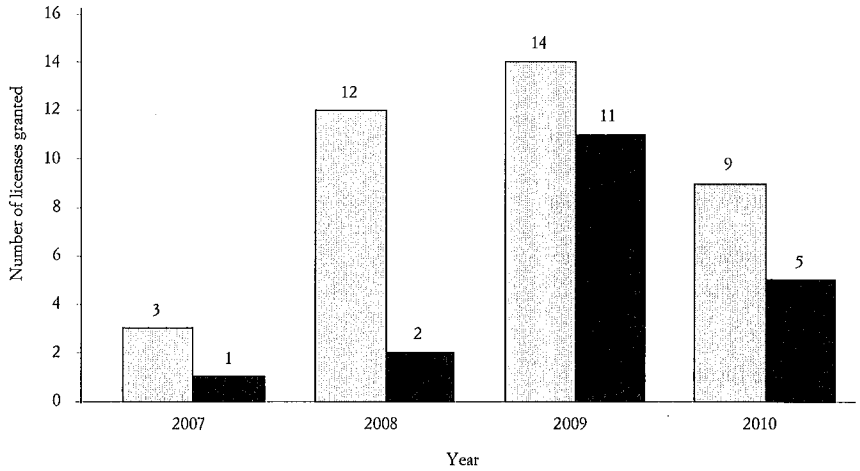
Provider	Number of hESC lines	Name of hESC lines
BresaGen, Inc. (Division of Novocell), Athens, GA, USA)	3	BG01, BG02, BG03
Cellartis AB, Göteborg, Sweden	7	SA01, SA02, **SA121**, **SA167**, **SA181**, **SA348**, **SA461**
ES Cell International Ltd, Singapore	6	ES01, ES02, ES03, ES04, ES05, ES06
Harvard University, Cambridge, MA, USA	7	HUES1, HUES2, HUES4, HUES6, HUES7, HUES8, HUES10
Karolinska Institute, Stockholm, Sweden	3	**HS181**, **HS401**, **HS415**
Kyoto University, Kyoto, Japan		KhES-1, KhES-2, KhES-3
Centre for Life, Newcastle Fertility Centre, Newcastle, UK	2	**NCL-3**, **NCL-4**
University of Sheffield, Sheffield, UK	3	**Shef-1**, **Shef-2**, **Shef-3**
Technion, Israeli Institute of Technology, Haifa, Israel	4	TE03, TE04, TE06, TE07
Wisconsin Alumni Research Foundation (WARF), WiCell, Madison, WI, USA	5	WA01, WA07, WA09, WA13, WA14

Twenty hESC lines were derived before the original cut-off date stipulated in the Stem Cell Act (1 January 2002), while 23 cell lines (in bold) were derived between 1 January 2002 and 1 May 2007 (the cut-off date as determined by the amended Stem Cell Act of August 2008). Note that the validation whether a specific hESC line meets the criteria of article 4 of the German Stem Cell Act is only performed after an application for import and use of this hESC line has been filed. It is estimated that a large number of additional hESC lines might also meet the criteria of the Stem Cell Act.

Source: Robert Koch Institute, www.rki.de

research on genetic and epigenetic networks that control pluripotency, induction of pluripotency by nuclear reprogramming, and mathematical modelling of pluripotency. Besides this program, the DFG is supporting further stem cell research projects submitted as single project proposals and undertaken within other programs.

Figure 3. *Use of hESCs and hiPSCs in research approved by the Robert Koch Institute (RKI) and the Central Ethics Committee for Stem Cell Research (ZES) from 2007 to 2010*



Shown are the numbers of hESC research licenses granted in recent years (light grey bars) and the numbers of approved hESC projects which also involve the use of hiPSCs (dark grey bars).

Source: Robert Koch Institute, www.rki.de

One of these programs is called *Regenerative Therapies: From Cells to Tissues to Therapies* pursued at the Center for Regenerative Therapies in Dresden (CRTD). The program started in 2006 and comprises working groups at the University of Technology (TU) Dresden, the Biotechnology Center, the Max-Planck-Institute on Cell Biology and Genetics (MPI-CBG), the Max-Bergman Center for Biomaterials, and the Medical Theoretical Center. The main concerns of the research projects are haematology, oncology, immunology of stem cells, diabetes, neurodegeneration, hard tissue replacement and cardiovascular diseases, while only a few projects are working with human ESCs.

In 2006, the CRTD was nominated a «Cluster of Excellence» and received additional support from the DFG within the DFG Excellence Center Engineering the Cellular Basis of Regeneration. Moreover, stem cell groups at the Hanover Medical School obtained funding within the Excellence Cluster from Regenerative Biology to Reconstruction (REBIRTH).

Table 3a. *Number of applications and approvals for the funding of projects in the field of stem cell research in Germany by the German Research Foundation (2000-2009)*

	DFG-funded stem cell projects including research on hES cells				
	Applications		Approvals		Funding (total)
Year	Single Applications	Projects within framework programs*	Single Applications	Projects within framework programs*	Approved (Million €)
2000	46	12	22	6	3,11
2001	79	9	36	8	4,89
2002	93	10	37	7	3,94
2003	99	13	42	9	5,96
2004	91	14	35	12	4,25
2005	115	13	60	9	11,75
2006	112	26	41	15	9,40
2007	107	15	47	11	9,94
2008	152	19	73	14	20,05
2009	132	20	69	16	20,60

* The number correlates with the number of different framework programs.

Source: DFG

The Federal Ministry of Education and Research (BMBF) has supported a number of initiatives in regenerative medicine, such as the Organ Substitution and Cell-Based Regenerative Medicine programs, and research on Pluri- and Multipotent Stem Cells (see table 4). In addition, two Translational Centers for Regenerative Medicine (TRM) at Berlin and Leipzig are supported with 7.5 million EUR each. A total amount of at least 270 million EUR has been spent by the BMBF for basic and applied research in the field of regenerative medicine, including stem cell research. While most projects deal with human or animal somatic stem or progenitor cells, animal ES cells and induced pluripotent stem (iPS) cells, only a small proportion (7.8%) of projects involve hESCs.

A new reference centre for stem cell research, the Center for Applied Regenerative Developmental Technologies (CARE), has been recently founded in Münster. Over the next decade, this centre will be funded with a total of 80 million EUR by the *Land* North Rhine-Westphalia (60 million) and the BMBF (20 million). The Max-Planck Society will also contribute funding.

Table 3b. *Number of applications and approvals for the funding of projects in the field of hESC research in Germany by the DFG (2000-2009)*

	DFG-funded projects on hESCs on				
	Applications		Approvals		Funding (total)
Year	Single Applications	Projects within framework programs*	Single Applications	Projects within framework programs*	Approved (Million €)
2000					
2001					
2002	1	1	1	1	0,22
2003	1	0	1	0	0,23
2004	4	2	3	2	0,51
2005	4	1	3	1	0,68
2006	6	1	2	1	0,20
2007	4	0	2	0	0,46
2008	7	3	3	2	1,06
2009	14	0	4	0	1,75

* The number correlates with the number of different framework programs.

Source: DFG

Table 4a. *Project applications submitted to the Federal Ministry of Education and Research (BMBF) within specific calls of unit 615 (Health Research)**

Announcement (Year)	1999	2004	2007	2008	2009
Topic of research (main focus)	Organ substitution	CRM1	PMSC1	CRM2	PMSC2
Number of projects	182	332	123	251	104
Number of grants	32	47	29	57	22
Funding applied for (Million €)	79	96	48	82	41
Funding granted (Million €)	10	12	9	19	6
Funding period	2001-06	2005-09	2008-12	2009-12	2010-13

* Research programs: Organ substitution = Biological substitution of organ functions. Given are the number of project applications, grants and the amount of funding in Millions of EUR.

Source: BMBF

Table 4b. *Funding of stem cell research within specific calls of the BMBF in Millions of EUR**

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Organ substitution	1	2,6	3,4	2.2	0,6	0,1				
CRM1					0,8	3,9	3,9	3	0,4	
CRM2									1,9	5,8
PMSC1								0,4	2,5	2,6
PMSC2										0,7
Sum	1	2,6	3,4	2,2	1,4	4	3,9	3,4	4,8	9,1

Source: BMBF

Table 4c. *Cell types used in research programs funded by the BMBF. Shown is the funding in Million EUR**

	Organ substitution (1999)	CRM1 (2004)	PMSC1 (2007)	CRM2 (2008)	PMSC2 (2009)	Sum
Human ES cells	3	15	0	3	0	21
Animal ES cells	8	16	0	4	0	28
Human somatic stem and progenitor cells	16	28	3	32	15	94
Animal somatic stem and progenitor cells	14	15	6	39	2	76
Germ-line derived cells	0	0	6	11	0	17
iPS cells	0	0	14	11	9	34

Total: ~ 270 Million EUR

* Abbreviations: CRM1 = Cell-based regenerative medicine, Phase 1; CRM2 = Cell-based regenerative medicine, Phase 2; PMSC1 = Pluri- and multipotent stem cells, Phase 1; PMSC2 = Pluri- and multipotent stem cells, Phase 2; iPS cells = induced pluripotent stem cells.

Source: BMBF

V. Pluripotent stem cell research in Germany in comparison to international research

According to the Stem Cell Act, all projects that involve hESCs must be listed in a public registry located on the web pages of the Robert Koch Institute[13]. This register allows the identification of research areas and topics of hESC research in Germany. Most of the projects deal with basic research and pursue the following aims: 1. Establishment and optimization of *in vitro* cultivation, purification and genetic modification of hESCs, 2. Analysis of molecular regulation of pluripotency and characterization of signalling networks controlling pluripotency, 3. Differentiation of hESCs towards differentiated derivatives, such as neural, cardiac, liver, blood, bone, lung or pancreatic cells, and 4. Studies using hESCs in comparison to other pluripotent stem cells, such as iPS cells or spermatogonial stem cells.

As mentioned above, out of the more than 1300 hESC lines established by the end of 2010 (see table 5), usable in Germany are only those cell lines that have been established before May 2007 and comply with the other stipulations of the Stem Cell Act (see table 2). However, the Stem Cell Act also precludes the import and use of cell lines derived from embryos no longer used for reproductive purposes for reasons inherent to the embryos themselves. Not allowed, therefore, is the import and use of human ESCs derived from IVF embryos analysed by preimplantation genetic diagnosis (PGD) for potential hereditary diseases. Consequently, the at least 166 hESC lines that carry mutations causative of 46 inheritable human diseases («disease-specific hESC lines», table 6) currently existing cannot be used for research in Germany. However, it is generally accepted that research using these hESC lines may be valuable to gain deeper understanding of pathogenesis mechanisms and to identify novel diagnostic and therapeutic strategies for the respective diseases.

Since 2004, scientists involved in hESC research in Germany have published a number of papers. However, by the end of 2009, only 23 original papers describing experimental work involving hESCs had been published by German researchers in English-language journals indexed in PubMed. Only four of these papers resulted from projects

[13] http://www.rki.de/DE/Content/Gesund/Stammzellen/Register/register_node.html

Table 5. *Overview of hESC lines publicly reported by the end of 2010*

Country	Number of hESC lines	Number of institutions	Number of hESC lines published in the scientific literature
Australia	69	4	25
Belgium	47	3	29
Brazil	1	1	0
Canada	6	2	4
China (incl. Taiwan)	270	16	261
Czech Republic	7	1	4
Denmark	31	4	14
Finland	14	2	12
France	24	5	14
India	17	4	7
Iran	10	1	10
Israel	30	3	28
Japan	3	1	3
Korea	37	5	35
Netherlands	4	1	4
Russia	16	2	5
Singapore	15	2	15
Spain	26	4	22
Sweden	90	3	45
Switzerland	4	2	1
Thailand	1	1	1
Turkey	18	1	16
United Kingdom	50	9	35
United States	516	22	225
Total (24 Countries)	1306	99	815

The numbers of institutions at which hESC lines were derived and of hESC lines reported in peer-reviewed publications are also given. Cell lines derived by the Reproductive Genetics Institute (Chicago IL) and partially distributed by Stemride International Limited (London, UK) have been assigned to the United States. hESC lines from ES Cell International Ltd. have been assigned to Singapore.

Source: Ref. 14 and unpublished data

funded by the DFG. When considered in the international context and compared to other countries, primarily the United States and the United Kingdom, the 23 original publications from hESC studies performed in Germany is only a small number. To date, German hESC research has accounted for only 1.7% of total publications on hESCs worldwide. Other countries, such as Israel, South Korea, Singapore, China, Australia, Japan, Canada and Sweden, are much more produc-

Table 6. *hESC lines with genetic disorders causative of inheritable human diseases («disease-specific» hES cell lines) as reported in the scientific literature by the end of 2010*

Genetic Disorder	Number of hESC lines
Adrenoleukodystrophy	1
alpha-Thalassaemia	2
Alport Syndrome	2
Androgen Insensitivity Syndrome (AIS)	2
beta-Thalassaemia	8
Charcot-Marie-Tooth syndrome	5
Cystic fibrosis (CF)	21
Dystrophya myotonica type 1 (DM1)	8
Fabry Syndrome	1
Facio Scapulo Humeral (FSH) muscular dystrophy	10
Familial adenomatous polyposis (FAP)	3
Familial breast cancer (BRCA1)	1
Familial breast cancer (BRCA2)	1
Fanconi anaemia	1
Fragile X syndrome (FX)	15
Gaucher's disease	1
Hemophilia A	1
Huntington's disease (HD)	15
Infantile Neuroaxonal Dystrophy	1
Marfan syndrome (MFS)	4
Multiple endocrine neoplasia type 1	2
Multiple endocrine neoplasia type 2	4
Multiple exostoses type 2	1
Muscular dystrophy, type Becker	2
Muscular dystrophy, type Duchenne	6
Muscular dystrophy, type Emery Dreifuss	4
Myotonic dystrophy (unspecified)	2
Myotubular myopathy (MTM)	2
Neurofibromatosis	2
Neurofibromatosis type 1	7
Ocular albinism	2
Osteogenesis imperfecta type 1	1
Pelizaeus-Merzbacher Disease (PMLD)	1
Polycystic Kidney Syndrome	1
Popliteal Pterygium Syndrome (PPS)	1
Saethre-Chotzen Syndrome (Acrocephalosyndactyly Type 3, ACS III)	1
Sandhoff disease	3
Sickle cell anaemia	3
Spastic paraplegia type 4	1
Spinal muscular atrophy type 1 (SMA1)	2

Spinocerebellar Ataxia Type 2 (SCA2)	1
Spinocerebellar Ataxia Type 7 (SCA7)	1
Torsion dystonia (DYT1)	4
Treacher Collins-Franceschetti Syndrome (TCOF), affected	2
Tuberous sclerosis	4
Von Hippel-Lindau (VHL) Syndrome	3
Total: 46 genetic disorders	166

Source: Ref. 14 and unpublished data

tive in this research field (see table 7)[14]. Moreover, the impact of hESC research papers from Germany is lower than that of papers produced in other countries. For example, research papers from the United States reporting experimental work involving hESCs and published between 2004 and 2008 had an average citation frequency of 48.0 citations per paper in 2009, and papers from Israel, Canada and the UK published in the same period were cited an average of 42.8, 35.9 and 36.7 times in 2009, respectively. By contrast, hESC research papers from Germany were cited an average of 21.6 times in 2009. The reasons for the lag of German hESC research have not yet been investigated in detail. Reservations in regard to hESC research by a part of the policy community and the general public, the relatively low funding, and the restrictions in view of the commercial use of hESCs may have contributed to the relatively weak international position of German hESC research.

By contrast, research involving hiPSCs was warmly welcomed even by those parts of the public and the policy community that regarded hESC research critically for ethical, religious or ideological reasons. Human iPSC research is considered to be «free» of ethical problems because no embryo destruction is necessary to provide human pluripotent stem cells. However, Germany's contributions in this scientific field were still limited by the end of 2009. Whereas research groups in the United States and Japan had published 60 and 16 original research papers on hiPSCs, respectively, only 3 publications came from German research groups (see table 8). It will be interesting to see whether Germany will strengthen its position in this novel research field within the next years, or whether the scientific backlog in ESC research will have a negative impact on the development of hiPSC research in Germany.

[14] P. LÖSER et al., *Human Embryonic Stem Cell Lines and Their Use in International Research*, in «Stem Cells», 28, 2010, pp. 240-246.

Tab. 7. *Numbers of hESC research papers published between 1998 and 2009*

Country	Number of hESC papers	% of total hESC papers
Australia	52	3,8
Austria	1	0,1
Belgium	17	1,2
Brazil	1	0,1
Canada	40	2,9
China	69	5,0
Czech Republic	7	0,5
Denmark	10	0,7
Estonia	1	0,1
Finland	15	1,1
France	18	1,3
Germany	23	1,7
Hungary	2	0,1
India	17	1,2
Iran	10	0,7
Israel	81	5,9
Italy	12	0,9
Japan	50	3,6
Korea	70	5,1
Netherlands	16	1,2
Portugal	1	0,1
Romania	1	0,1
Russia	6	0,4
Singapore	71	5,2
Spain	18	1,3
Sweden	54	3,9
Switzerland	8	0,6
Thailand	1	0,1
Turkey	5	0,4
United Kingdom	112	8,1
United States	588	42,7
Total	1377	100

Given are the number of original research papers published in peer-reviewed English language journals and the share of work from a country in the total number of hESC papers. According to published work, hESC research is being carried out in at least 31 countries. Assignment of a paper to a country has been according to the corresponding author's address. Only work involving experimental use of hESCs has been included, whereas reviews, comments and papers reporting previously published methods or legal and ethical aspects of hESCs have been omitted.

Source: Ref. 14

Table 8. *Number of papers on derivation and/or experimental use of hiPSCs published from 2007 to 2009 in peer-reviewed English language journals*

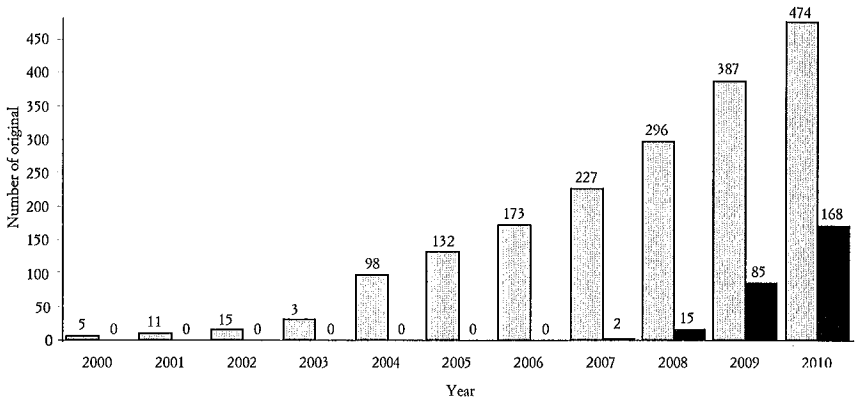
Country	Number of hiPSC papers	Share in total hiPSC papers
Canada	3	2,9
China	7	6,9
France	1	1,0
Germany	3	2,9
Iran	1	1,0
Israel	1	1,0
Japan	16	15,7
Spain	5	4,9
Switzerland	1	1,0
United Kingdom	4	3,9
United States	60	58,8
Total	102	100

Given are the number of original research papers and the share of work from a country in the overall number of hESCs papers. According to published work, hiPSC research was carried out in at least 11 countries by the end of 2009. Note that papers that were published online 2009, but appeared in print in 2010 are not included.

Source: Ref. 14 and unpublished data

One reason advanced by the proponents of hiPSC research who object to hESC research is that hiPSCs may very soon replace hESCs in research. However, a comparison of international activities in both research fields does not support this assumption (see figure 4). In 2010, the number of both peer-reviewed hESC and hiPSC research papers published in English-language journals increased further. Notably, a large proportion of papers on hiPSCs also involved the parallel use of hESCs either for comparative purposes or to investigate a scientific question in this cell type before the methods are applied to hiPSCs. Therefore, by the end of 2010 both research fields existed independently, had been further extended and partially overlapped.

Figure 4. *Numbers of papers reporting derivation and/or experimental use of hESCs (light grey bars) and hiPSCs (dark grey bars) as published by 10 December 2010 in peer-reviewed English language journals*



Note that the numbers for 2010 are preliminary and also include papers that were published online in 2010 but will appear as printed papers only in 2011.

Source: Ref. 14 and unpublished data

VI. Conclusion

Research on hESCs is an internationally well-accepted and rapidly expanding research field. Since the first publications on hESCs in 1998, research on hESCs has become internationally established as one of the new scientific disciplines now developing exponentially. Worldwide, a constant increase is apparent both in the number of newly established hESC lines and in the number of publications on those cells.

In Germany, hESC research is regulated by the Stem Cell Act of 2002 and its amendment of 2008. On the basis of the Stem Cell Act, research with hESCs is possible in Germany if the cells have been established before the cut-off date of May 2007, if the projects serve research goals of premium value, and if there is no alternative to the use of hESCs. When comparisons are made with other countries, specific conditions regulating hESC research in Germany should be considered: (1) human ESC research projects must be licensed in a two-step procedure that involves a governmental authority and an independent ethics committee;

(2) only research projects involving hESCs, but not the commercial use of these cells, are allowed by the Stem Cell Act; (3) although hESC projects are funded by German agencies, the level of funding is relatively low in comparison with other countries, specifically the United States or countries in the Asian-Pacific area. Consequently, the number of publications published on hESCs by German scientists is relatively small, and at present, the same applies to publications on hiPSCs.

On the other hand, certain advances have been achieved in Germany on the basis of legally regulated hESC research. Specifically, progress in human ESC and iPSC research in Germany has been driven by the continuous initiatives and activities of German researchers and the support of scientific bodies. With respect to international developments, research on hESCs has further expanded, and research on both hESCs and hiPSCs has been performed in parallel. At present, it is an open question whether hiPSC research will replace studies with hESCs in the future.

The Italian Case

Embedding Society in Cells: Science, Ethics and Politics in the Italian Public Debate on Stem Cell Research

by *Lorenzo Beltrame**

I. Introduction

Stem cell research is considered one of the most promising and revolutionary branches of contemporary biomedical research. However, it is also a much contested socio-political issue. Although there are several types of stem cells – depending on their differentiating plasticity and their location in the organism – public attention focuses predominantly on human embryonic stem cells (hESCs). Despite a long history and a complex genealogy within the life sciences[1], the starting point of a worldwide public debate on stem cells can be dated to November 1998, when James Thomson's research team successfully isolated and cultivated human embryonic stem cells derived from the inner cell mass of human embryos[2]. This breakthrough focused public attention on two competing social values: the therapeutic promise and the embryo question[3], that is, the possible future benefits of hESC research versus the controversial status of the human embryo and its legal tutelage.

Usually, the public debate on stem cell research is explained as the contrast between the moral status of the human embryo and the needs and hopes of (ill) people, who might benefit from stem cell-based therapies in the near future. On the one hand, there are those who

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1 See A. Dröscher in this book.

2 J.A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, in «Science», 282, 1998, pp. 1145-1147.

3 B. Rubin, *Therapeutic Promise in the Discourse of Human Embryonic Stem Cell Research*, in «Science as Culture», 17, 2008, 1, pp. 13-27.

posit that the human embryo should be considered a person from the moment of conception and, accordingly, must be protected in the name of the ethical principle of human dignity. On the other hand, there is an entirely different ethical position which holds that the key value in contemporary societies is the improvement and protection of (ill) people's health conditions. This «ethics of healing» (as opposed to the so-called «ethics of human dignity»)[4] resonates with a central feature of contemporary biopolitics: that our biological existence is an organizing principle of political action by which people claim identities, rights and services[5]. The legitimization of the state also depends on the effectiveness of responses to these healthcare demands[6].

As several scholars have noted, the embryo question has dominated the public debate to the point that an entire range of concerns, problems, and opportunities to do with innovations in stem cell science have been overlooked[7]. Therefore, policy-making in the field of stem cell research is usually viewed as a balancing among different and contrasting ethics, values, and interests in a context of heated controversy. National regulations on stem cell research broadly range from very restrictive normative frameworks (which substantially ban hESC research) to the opposite extreme of more liberal legislations resulting from a moral trade-off between the two ethical principles of human dignity and therapeutic promise[8].

Nevertheless, another distinguishing feature of the stem cell debate is its polarization between embryonic and adult stem cells (ASCs, a shared shorthand for a wide range of different stem cell types). Therefore,

[4] F.S. Oduncu, *Stem Cell Research in Germany: Ethics of Healing vs. Human Dignity*, in «Medicine, Health Care and Philosophy», 6, 2003, 1, pp. 5-16.

[5] N. Rose - C. Novas, *Biological Citizenship*, in A. Ong - S.J. Collier (eds), *Global Assemblage. Technology, Politics, and Ethics as Anthropological Problems*, London 2005, pp. 439-463.

[6] N. Rose, *The Politics of Life Itself*, London 2007.

[7] S. Parry, *The Politics of Cloning: Mapping the Rhetorical Convergence of Embryos and Stem Cells in Parliamentary Debates*, in «New Genetics and Society», 22, 2003, 2, pp. 145-168; B. Salter, *Bioethics, Politics and the Moral Economy of Human Embryonic Stem Cell Science: The Case of the European Union's Sixth Framework Programme*, in «New Genetics and Society», 26, 2007, 3, pp. 269-288.

[8] B. Salter, *Bioethics, Politics*, pp. 274-275.

regulating stem cell research implies not only defining the status of the human embryo, its rights and legal protection, but also the choice between different research trajectories based on the preferred stem cell sources and usually summarized in the above-mentioned polarization. As I shall show in this essay, this polarization has been highly influential in the regulation of stem cell research in Italy.

In what follows, I shall analyze the Italian debate on stem cell research, my purpose being to explain the particular trajectory of Italian stem cell regulation. I hold that, as in any other country, regulations in Italy are the outcome of a struggle among different views on stem cell research, and this struggle is fought by framing stem cells and stem cell research within interpretive repertoires which cluster and organize cultural and social elements (such as moral values, social goals, political identities, and ideas about the social role of science and religion). Such repertoires identify not only the political approaches to the regulation of stem cell research (and the preferred stem cell sources on which research is allowed), but also the foundational elements of the social order, that is, what kind of ethical values the state should protect, and what kind of social goals and interests it should promote. As the effect of an embedding process, the two competing research trajectories (hESC versus ASC research) have become representative of two different views of Italian polity, social order and national cultural identity. In the next section I shall clarify the analytical framework and the methodology used. The following sections will be devoted to the analysis of certain key moments in the Italian stem cell debate.

II. Co-production, discourses and the process of embedding

A central concern for scholars of social studies of science is the emerging legal and normative frameworks with which national governments, parliaments and other agencies regulate stem cell research and the surrounding heated political, ethical and scientific debates. As Prainsack et al. have pointed out, national responses to stem cell research are «impressive yet elusive», because «adjacent, modern, industrialized, otherwise similar European nations»[9] regulate stem cell research in

[9] B. Prainsack - I. Geesink - S. Franklin, *Stem Cell Technologies 1998-2008: Controversies and Silences*, in «Science as Culture», 17, 2008, 4, pp. 351-362, here p. 352.

very different ways[10]. How can these differences be explained? What does a national legal framework reveal about the specific configuration of relationships among science, politics, ethics, and culture in a given country?

According to, Jasanoff particular pathways in regulating biotechnologies rely on what she calls political culture, that is, the

«systematic means by which a political community makes binding collective choices ... institutionally sanctioned modes of action ... the myriad unwritten codes and practices with which a polity supplements its formal method of assuring accountability and legitimacy in political decisionmaking»[11].

Yet political cultures should not be considered as deterministic causal factors – just as I do not consider other structural cultural variables like the rate of religiosity to be such[12]. Rather, they should be regarded as situational and institutional characteristics which, on the one hand, delimit the range of action of the actors involved in debates, and on the other, are liable to modification by those actors according to their resources, strategies, and power. Stem cell regulations can be seen as the outcome of a struggle between different groups of actors, which, in defining their political strategies and their cultural framings of stem cell research, claim and try to impose socio-political identities, values, beliefs, goals and, in general, specific views on the social order linked to the framing of stem cells. Regulations on stem cell research can be explained by looking at the discourses of the relevant actors in the political-regulatory realm[13], since discourses provide novel bio-objects with interpretations and meanings, and connect them to general cultural

[10] H. GOTTWEIS - B. SALTER - C. WALDBY, *The Global Politics of Human Embryonic Stem Cell Science: Regenerative Medicine in Transition*, London 2009.

[11] S. JASANOFF, *Designs on Nature*, Princeton NJ 2005, p. 21.

[12] Religious beliefs are instead considered elements mobilized in the actors' discourses, rather than being direct causal factors; and religious institutions are, in their turn, actors involved in the debate. See also B. PRAINSACK, *'Negotiating Life': The Regulation of Human Cloning and Embryonic Stem Cell Research in Israel*, in «Social Studies of Science», 36, 2006, 2, pp. 173-205; B. PRAINSACK - R. GMEINER, *Clean Soil and Common Ground: The Biopolitics of Human Embryonic Stem Cell Research in Austria*, in «Science as Culture», 17, 2008, 4, pp. 377-395.

[13] H. GOTTWEIS, *Stem Cell Policies in the United States and in Germany: Between Bioethics and Regulation*, in «Policy Studies Journal», 30, 2002, 4, pp. 444-469, here p. 445.

themes (such as ethical principles, moral values and expectations)[14]. Policy-making is thus a performative process aimed at configuring a (local and temporary) arrangement of the social order.

This means that regulatory frameworks can be analyzed through the interpretive lens of the so-called «co-productionist account»[15]. According to Jasanoff, «co-production is shorthand for the proposition that the ways in which we know and represent the world (both nature and society) are inseparable from the ways in which we choose to live in it»[16]. That is, scientific knowledge is simultaneously a product of social work and constitutive of forms of social life, so that «it both embeds and is embedded in social practices, identities, norms, conventions, discourses, instruments and institutions»[17]. Put in other terms, when conditionalities and contexts of stem cell research are debated, actors establish identities, values, social goals and hierarchical relationships among social domains and institutions[18].

Related to co-production mechanisms is what can be termed an «embedding process». In the case of Italian stem cell debate the polarization between hESC research and ASC research has embedded different and competing views of social order. That is, cultural, political and ethical views are so entangled in the scientific evaluations of these two different families of stem cell sources that the struggle between diverging views on the social order are fought through technical discourses on the therapeutic effectiveness of stem cell sources. In other words, when deciding which line of research may be allowed, policy-makers and the other relevant actors also decide in what kind of social order they would want to live. The embedding of 'the social' in a biological discourse[19]

[14] H. GOTTWEIS, *Governing Molecules: The Discursive Politics of Genetic Engineering in Europe and the United States*, Cambridge 1998.

[15] S. JASANOFF, *The Idiom of Co-Production*, in S. JASANOFF (ed.), *States of Knowledge. The Co-production of Science and Social Order*, New York 2004, pp. 1-12.

[16] *Ibidem*, p. 2.

[17] *Ibidem*, p. 3.

[18] B. PRAINSACK et al., *Stem Cell Technologies*, pp. 353-354.

[19] This is an extension of Sarah Franklin's contention that, in contemporary society, «the social is literally being reinstalled *within* the biological». S. FRANKLIN, *Culturing Biology: Cell Lines for the Second Millennium*, in «Health», 5, 2001, 3, pp. 335-354, here p. 342. See also S. FRANKLIN, *Stem Cells R Us: Emergent Life Forms and the Global*

is possible because, according to Jasanoff, co-production operates at the level of discourses with which actors

«give accounts of experiments, persuade sceptical audiences, link knowledges to practice or action, provide reassurance to various publics, and so forth ... In the process, scientific language often takes on board the tacit models of nature, society, culture or humanity that are current at any time within a given social order»[20].

In other words, the elements of the social order are made manifest in discourses through the use of a scientific and/or science-like language. On the one hand, these social elements shape scientific evaluations of stem cells; on the other, scientific language provides these social elements with a bioscientific anchorage and a cognitive legitimization.

In light of this analytical framework I shall seek to explain the emergence of Italian regulations on stem cell research by linking the evolving discourses used in the debate to the normative and policy choices in several institutional *fora*. I shall analyze the discourses present in three main public spaces: mass media, documents of bioethical and experts' advisory committees, and regulatory and legislative institutions. The rationale for this choice is that stem cells emerged as an issue in the mass media before they did so in regulatory and political arenas. In the mass media public sphere actors framed stem cells and linked them to general representation of the social order (i.e., ethical values, legitimate collective goals, social interests and expected configurations of social structure with defined relations among institutions such as science, religion and politics). These envisaged social orders, or «imagined communities» in Benedict Anderson's terms[21], should be made binding by their implementation into normative devices which establish a particular research trajectory as legitimate. Because this trajectory embeds elements of an envisaged social order, it defines a (temporary and local) arrangement of the Italian polity structure.

I shall report analysis conducted on the discourses of relevant actors in the three most widely-circulating Italian newspapers – «Corriere della

Biological, in A. ONG - S.J. COLLIER (eds), *Global Assemblage. Technology, Politics, and Ethics as Anthropological Problems*, London 2005, pp. 59-78.

[20] S. JASANOFF, *Ordering Knowledge, Ordering Society*, in S. JASANOFF (ed.), *States of Knowledge. The Co-production of Science and Social Order*, New York 2004, pp. 13-45, here pp. 40-41.

[21] B. ANDERSON, *Imagined Communities*, London - New York 1991.

Sera», «La Repubblica», and «La Stampa» – and the main fora for social actors opposed to hESC research – «Avvenire» (the newspaper of the Italian Bishops' Conference) and «Il Foglio». After the analysis of key actors' framing of stem cells in the mass media public sphere[22], I then analyzed documents of bioethical and expert advisory committees (e.g. the Pontifical Academy for Life, the National Bioethics Committee and the so-called Dulbecco Commission) and, finally, the stenographic transcriptions of the parliamentary debate on the Italian law on medically assisted fertilization, which also regulates human cloning and embryo research. By so doing, I sought to reconstruct the evolution of the discourses over ten years and in various public and political spaces.

III. From non-problematic objects to a highly controversial issue

Usually, novel biological objects are socially problematic entities because they tend to call foundational cultural categories into question[23]. This was the case of the first human embryo created in vitro, which blurred the cognitive and cultural boundary between natural and artificial. As Douglas has shown, the social order of any human society is founded on a set of cultural boundaries ordering events, objects, and subjects[24]. When the classifications comprising the social order are disrupted by the emergence of problematic objects, actors must restore this order. In this sense, the framing of emerging objects can be interpreted as a political task undertaken to repair the symbolic order of reality[25].

[22] My interest will not be in journalistic discourse in itself, nor in the relations between mass media frames and public perceptions of stem cell research. I shall adopt the «public arenas model» developed by Hilgartner and Bosk which considers mass media to be spaces used to make discourses public (sorts of 'sounding boards' with which actors broadcast their frames of the issue and seek to obtain public consensus on their positions) and, therefore, as depositories of narratives and interpretations made by important actors involved in the debates. See S. Hilgartner - C.L. Bosk, *The Rise and Fall of Social Problems: A Public Arenas Model*, in «American Journal of Sociology», 94, 1988, 1, pp. 53-78.

[23] S. Jasanoff, *Designs on Nature*.

[24] M. Douglas, *Purity and Danger. An Analysis of the Concepts of Pollution and Taboo*, London 1966.

[25] B.P. Bloomfield - T. Vurdubakis, *Disrupted Boundaries: New Reproductive Technologies and the Language of Anxiety and Expectation*, in «Social Studies of Science», 25, 1995, 3, pp. 533-551.

But this is not the case of stem cells. Stem cells appeared in the public arena of the Italian mass media at the beginning of the 1990s thanks to the work of the research team headed by Cesare Peschle[26]. Located only in blood and in bone marrow, stem cells were considered to hold out revolutionary promises for the therapy of blood diseases and hopes for transplants in an era dominated by the fear of HIV-contaminated blood. But stem cells were non-controversial objects; indeed, they were discussed in medical and science news reports, without problematic connections with ethical and social concerns.

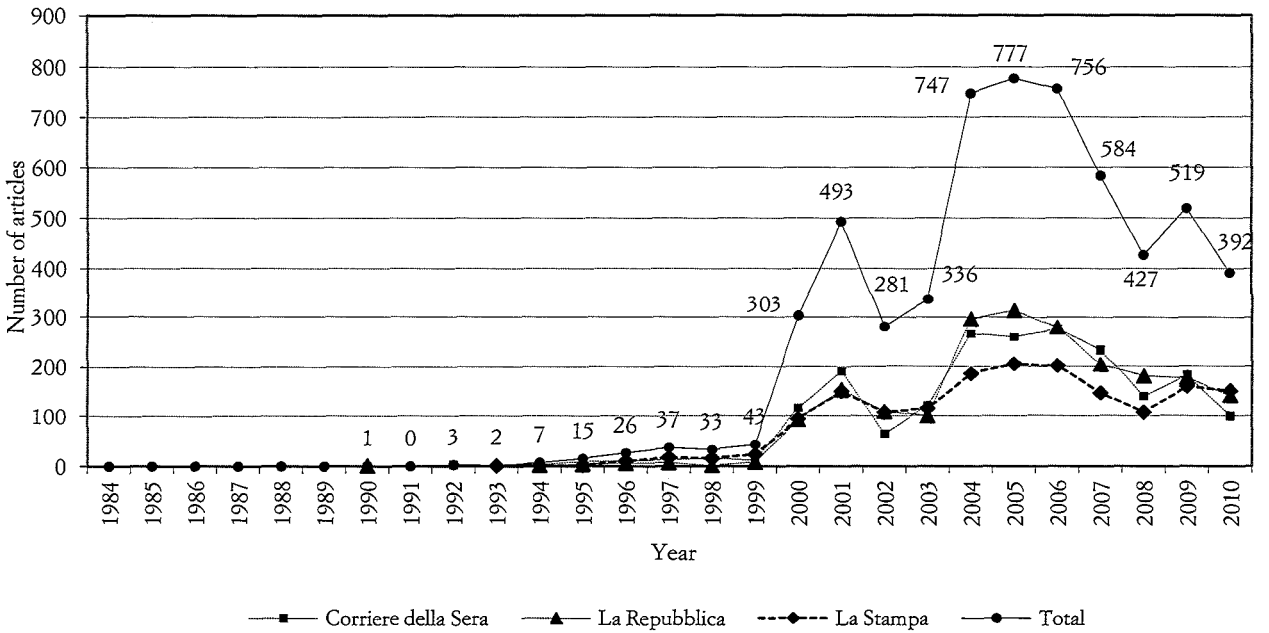
Figure 1 reports the number of articles dealing with stem cells published by «Corriere della Sera», «La Repubblica» and «La Stampa»[27], and shows how, during the 1990s, stem cells constituted an issue with low media coverage. For example, the famous breakthrough by Thomson's research team – considered the starting point of the worldwide stem cell debate – received scant attention from the Italian newspapers. This does not mean that regenerative medicine was unknown in that period; rather, that it was discussed within the frame of cloning, and using the vague expression «manipulation of embryos». During the 1980s, cloning was constructed in the public imagery as the ultimate bioethical limit, the most radical form of manipulation of embryos, not only in science fiction literature and films[28], but also in newspapers articles and in two important bioethical documents – the *Instruction Donum Vitae* of the Roman Catholic Church's Congregation for the Doctrine of the Faith, and the document *Identità e statuto dell'embrione* (*Identity and Status of the Human Embryo*) issued by the Italian National

[26] M. GABBIANELLI et al., *«Pure» Human Hematopoietic Progenitors: Permissive Action of Basic Fibroblast Growth Factor*, in «Science», 249, 1990, 4976, pp. 1561-1564.

[27] The key period of the stem cell debate started in 1998, but because «La Repubblica» has a systematic electronic archive which contains all articles published since 1984 (the year of the first Italian test-tube baby), I used «La Repubblica» to map the evolving discourse on stem cell and related issues, such as cloning, embryo research and medically assisted fertilization before 1998. Articles published by the other newspapers were used only for qualitative discourse analysis in key periods of the Italian debate.

[28] In particular Aldous Huxley's *Brave New World* and Ira Levin's *Boys from Brazil*. On the role of popular literature in shaping the public perception of science see J. TURNEY, *Frankenstein's Footsteps. Science, Genetics and Popular Culture*, New Haven CT 1998.

Figure. 1. *Articles dealing with stem cells published in «Corriere della Sera», 1992-2010, «La Repubblica», 1984-2010, «La Stampa», 1992-2010, and total number of articles dealing with stem cells (1984-2010)*



Source: Author's elaboration

Bioethical Committee[29] – which defined cloning (together with other forms of manipulation of human embryos)[30] as being contrary to the dignity due to the human embryo. Cloning aroused anxiety and fear and, when on 5 March 1997, the then Minister of Health Rosy Bindi issued a ministerial decree which prohibited «any whatever form of experimentation and intervention, however undertaken, even indirectly, for the purpose of human or animal cloning» – no opposing voices were raised[31]. As a consequence, between 1984, the year of the birth of the first Italian test-tube baby, and August 2000, the emerging field of human biotechnologies was framed in what Mulkay has termed the «rhetoric of fear», a discursive repertoire which conveys a negative image of science especially when science and technology seem to violate basic cultural categories and moral values[32].

But in August 2000 matters suddenly changed. On 16 August 2000 the British Government decided to amend the Human Fertilization and Embryology Act (1990) in order to allow stem cell research on embryos left over IVF treatments or created by Somatic Cell Nuclear Transfer (SCNT). Although the first reactions were still focused on the theme of cloning, Italian public opinion exhibited the first explicit polarization between supporters and opponents.

The opponents included Catholic politicians and intellectuals, as well as members of the Roman Catholic Church and lay personalities (*laici*), such as Giovanni Berlinguer, a professor of biology, bioethicist and member of a left-wing party. The first reactions were characterized by evocative metaphors drawing on the rhetoric of fear, and by the

[29] CONGREGATION FOR THE DOCTRINE OF THE FAITH, *Instruction on Respect for Human Life in Its Origin and on the Dignity of Procreation. Replies To Certain Questions Of The Day (Donum Vitae)*, Vatican 1987; COMITATO NAZIONALE PER LA BIOETICA, *Identità e statuto dell'embrione umano*, Roma 1996.

[30] This generic and rather vague expression denoted various practices and techniques: cloning, parthenogenesis, twin fission, the creation of chimeras, and hybridization, but also the freezing of embryos, embryo selection, embryo donation and surrogate motherhood.

[31] As in the case of medically assisted fertilization, until the enactment of Law 40/2004, also cloning research was regulated at a sub-legislative level by repeatedly renewed decrees.

[32] M. MULKAY, *The Rhetoric of Hope and Fear in the Great Embryo Debate*, in «Social Studies of Science», 23, 1993, 4, pp. 721-742.

interpretive frame of a technoscience opposed to basic moral values. Frankenstein, Mengele and Nazi eugenics were among the literary and historical examples used to frame what Italian mass media called 'British decision'. A common feature of the discourses of opponents was the call for intervention by the European Union so as to regulate this research at supranational level and halt a dangerous moral drift which threatened human rights and European cultural identity. This appeal responded to an endeavour to extend universally regarded moral values which, in its turn, implied that only a supranational political institution could affirm such universality. But this argument also asserted the politicization of ethically controversial scientific issues and affirmed the primacy of traditional political arenas (i.e. parliaments) in ruling on such innovations.

This is a clear example of co-production. In the view of opponents, objecting to the use of human embryos – because, according to Cardinal Ersilio Tonini, «it is contrary to the *fundamental principle of our humanism and civilization*» («Corriere della Sera», 17 August 2000, emphasis added) – meant taking account of categories and values such as human rights, humanism, and civilization. These values were not only (re)affirmed in discourses; they were then (re)constructed and enacted through their mobilization in political action. Stem cell policies thus became constitutive elements in the construction of European cultural and political identity. This was made particularly clear in a statement by Giovanni Berlinguer, according to whom the British decision «runs counter to morality; in particular, that of Europe ... a continent philosophically founded on Christianity and Kant ... It is a mortal blow to the European Convention» («Corriere della Sera», 17 August 2000). The opposition to hESC research embedded a specific view of the social order, which celebrated and defended the conservation of ethical values considered foundational to the cultural identity of a given polity.

On the side of supporters of the British decision, most of whom were scientists, the reactions could be framed in the rhetoric of hope and the ethics of healing. Geneticist Giuseppe Novelli said «this is fantastic news, news which shows that in Great Britain the relationship between politics and science is at an advanced stage. It is, of course, fantastic news above all for those who suffer» («La Repubblica», 17 August 2000). The supporters highlighted the therapeutic promise of regenerative medicine in regard to the hopes of ill people. The prospects of

regenerative medicine were compared with the discovery of antibiotics, and it was claimed that new treatments for Parkinson's, Alzheimer's, and other diseases would be developed in the next five to ten years. Besides the theme of giving hope to the sick, some scientists also resorted to the rhetoric of scientific research as the preferred means to achieve (supposed and suggested) socially shared goals such as well-being, wealth, progress and competitiveness in a global knowledge economy. Biologist Edoardo Boncinelli maintained:

«today the wealth of nations and therefore their powers to act on the world stage are largely measured by their scientific and technical capacities. A country cannot close in on itself and constantly and systematically reject all developments and all prospects of a biotechnological nature» («Corriere della Sera», 24 August 2000).

Supporters of hESC research propounded a different view of social order which celebrated innovation and posited other ethical values as foundational to the Italian polity.

Whilst this opposition reflected the classic dichotomy between the therapeutic promise of hESC research and the alleged sacred status of the human embryo, some days after the first reactions to the British decision the discourse shifted to the polarization between hESCs and ASCs. After the US president Bill Clinton's decision to modify the regulations on embryo research, permitting the federal funding on research using stem cells derived from supernumerary embryos, Italian newspapers (improperly) began to talk about a «British way» to regenerative medicine – which implied human cloning – and an 'American way» – which was based on the use of human embryos left over from IVF treatments. The debate was then reframed into the question of what should be the 'Italian way' to stem cell research. This reframing gave prominence to the discourse on the differential capacity of stem cell types, involving a process of embedding in which ethical issues regarding the use and the status of human embryos were entangled with an apparently neutral technical discourse on the biology of stem cells.

On the one hand, there were those who claimed that the Italian way should consist in ASC research alone. For example, hematologist Girolamo Sirchia stated that

«research on embryos is not the only way forward. There is an alternative, and in a matter of years the ethical problem will be superseded because it will be possible to use adult stem cells ... a field in which Italian research is very advanced» («Corriere della Sera», 19 August 2000).

In similar vein, physician Raffaello Cortesini said that

«there are other ways forward, and we should insist on these. I refer to research on bone-marrow and umbilical-cord stem cells ... These are alternatives which would avert the ethical problems raised by use of the embryo, which is life and cannot be touched» («Corriere della Sera», 24 August 2000).

On the other hand, there were who suggested a sort of 'double track' for stem cell research, such as biologist Carlo Alberto Redi, according to whom

«the Italian solution should be to use human embryos (but only spared ones) while simultaneously investing in the 'alternative ways', also because Italian researchers are in forefront in this field» («Corriere della Sera», 24 August 2000).

Supporters of ASCs maintained that this kind of cells was a valid alternative to hESCs, and considered the latter as morally reprehensible. Supporters of hESCs, instead, defined ASCs as less therapeutically useful than hESCs. Nobel-prize winner Renato Dulbecco clarified this position in a leading article on «La Repubblica»:

«The use of [adult stem] cells would not raise the ethical problems that must be addressed when embryo cells are used ... adult stem cells are not yet well known. *They are more difficult to obtain* than embryo cells: *it is not known if they can be cultivated for a long time* in vitro without change to their properties: it seems that *their capacities for differentiation are inferior to those of embryo cells*, and the conditions for their practical use have not yet defined» (18 August 2000, Italics added).

ASCs were framed as a mere ethical alternative, a makeshift solution to the use of hESCs as less plastic and proliferating than the latter. Moreover, while ASC research seemed to require a long time in order to yield useful therapeutic applications, hESC research was described as «just around the corner»[33] for treatment-providers. On these bases, the ethical discourse was embedded in technical matters. Whilst ASCs complied with the ethics of human dignity – because they did not imply the use and destruction of human embryos – they failed to fulfil more broad therapeutic expectations attached to the representation of hESCs potential. In other words, technical issues (plasticity, proliferating and differentiating capacity, and therapeutic effectiveness) overlapped with ethical concerns. Deciding between these two families of stem

[33] See R. EVANS - I. KOTCHETKOVA - S. LANGER, *Just around the Corner: Rhetorics of Progress and Promise in Genetic Research*, in «Public Understanding of Science», 18, 2009, 1, pp. 43-59.

cell sources meant deciding what kind of ethical vision should be the founding principle of the Italian social order: the defence of the human dignity granted to the early human embryo or the improvement of (ill) people's health, the freedom of research, and the search for competitiveness in the global race for scientific leadership.

The definitive grounding of the stem cell debate in the polarization between adult and embryonic stem cells came about on 25 August 2000, when the Pontifical Academy for Life (PAL) released a document on stem cell research and the former minister of Health Umberto Veronesi issued an important declaration during the annual meeting of Communion and Liberation (a Catholic ecclesial movement highly influential in Italian political affairs).

The PAL's document, entitled *The production and the scientific and therapeutic use of human embryonic stem cell*, clarified the position of the Magisterium of the Roman Catholic Church on hESC research and on cloning: because such techniques implied the destruction of human embryos, they were immoral and should be prohibited in the name of the human dignity possessed by the human embryo, which was defined as «a human subject with a well defined identity» arising from «the union of the gametes», because at that point there «begins its own coordinated, continuous and gradual development»[34]. According to this embedding of ethics in a scientific discourse – i.e. the status of human embryo as resulting from a biological definition and a scientific evaluation of the embryogenesis and embryo development processes – PAL also proposed a preferential pathway for stem cell research based on the exploitation of adult stem cells:

«The progress and results already obtained in the field of adult stem cells (ASC) show not only their great plasticity but also their many possible uses, in all likelihood no different from those of embryonic stem cells ... The possibility, now confirmed, of using *adult stem cells* to attain the same goals as would be sought with embryonic stem cells ... indicates that *adult stem cells represent a more reasonable and human method for making correct and sound progress in this new field of research and in the therapeutic applications which it promises*. These applications are undoubtedly a source of great hope for a significant number of suffering people»[35].

[34] PONTIFICAL ACADEMY FOR LIFE, *The Production and the Scientific and Therapeutic Use of Human Embryonic Stem Cell*, Vatican 2000.

[35] *Ibidem*.

By means of an impressive amount of citations of scientific papers (including the work of the neurologist Angelo Vescovi on the trans-differentiation of adult stem cells[36]), PAL turned the image of ASCs from that of a makeshift solution to the forefront of therapies development, and, moreover, as the way to guarantee a «correct and sound progress».

On the same day as the release of this document, Italian Minister of Health Umberto Veronesi announced

«... I have created a committee of experts beyond any suspicion of influence which in some weeks time will give me their opinion ... on the extent to which the proposals contained therein can be reasonably transferred to our society ... the most effective stem cell is the fertilized egg ... Stem cells are important because, from this scientific perspective, they could cure – could, of course, because we cannot be certain – effectively and definitively persons suffering from those degenerative diseases ... In all the refrigerators of the thousand obstetric clinics in the world there are millions of frozen embryos ... What will be the fate of this mass of frozen embryos, of these potential men and women who will never become such? Given that these fertilized cells, these embryos, have the potential to enable people to live ... rather than throw them away, it is better to use them for therapeutic purposes»[37].

Apparent here are three central elements characterizing the discourse of supporters of hESC research. First, the definition of hESCs as having more therapeutic effectiveness than ASCs. Second, the framing of supernumerary embryos as exploitable experimental materials on the basis of an ethical evaluation which compares the destiny of spared embryos with the hopes and needs of the ill (i.e. the ethics of healing). Third, the announcement of the creation of an expert committee to evaluate the issues of stem cell research.

These events gave a political dimension to the emerging debate. On the one hand there was an important religious institution, which not only framed the stem cell topic by linking it with the Catholic Magisterium but also defined the embryo question (i.e. the human embryo as a person) and suggested a science policy based on the use of ASCs. On the other hand, there was a minister of the Italian state, a famous physician considered a spokesperson for the Italian scientific community but who, instead, declared himself in favour of the use of supernumer-

[36] C.R.R. Bjornson et al., *Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in Vivo*, in «Science», 283, 1999, pp. 534-536.

[37] *Libertà di salute. Sanità: tra centralismo e devoluzione*, Rimini, 25 August 2000, available on web: http://www.meetingrimini.org/default.asp?id=673&item=137

ary embryos left over from IVF practices (which were defined as only potential human beings) and appointed an expert advisory committee to formulate guidelines. On 25 August 2000, stem cell research became a fully political issue.

IV. The politics of cells and the governance of technoscientific innovations

It is useful to summarize the two main discursive formations in which ethical, political, and cultural elements were entangled and embedded in the apparently technical choice between adult and embryonic stem cells. As table 1 shows, these discursive formations can be described on the basis of the ethics affirmed, the definition made of the status of human embryo, the image of the social role of science propounded, and the policy tools proposed to regulate stem cell research.

Both discursive formations connected ethical elements to scientific arguments and, on the basis of these connections, proposed policy pathways to regulate stem cells. They thus envisaged social orders and sought to make them binding both at a legal and political level. Two different views of the role of politics and the state informed these discursive formations. Consequently, also the debate on policy tools, notwithstanding its technical nature, was entangled with different views on the social order, the relation between science and society, and Italian political identity. Furthermore, the stem cell debate raised the question of regulating technoscience, a topic long evaded by Italian politicians.

Whilst opponents of hESCs urged a fully political approach (i.e. a parliamentary ruling), Minister Veronesi proposed a policy approach in line with the pro-hESCs discourse: an expert commission with the task of proposing regulatory guidelines. On 7 September 2000, Umberto Veronesi officially appointed the Commissione di Studio sull'Utilizzo di Cellule Staminali per Finalità Terapeutiche (Study Commission on the Use of Stem Cells for Therapeutic Purposes), chaired by the Nobel Prize-winner Renato Dulbecco and known as the Dulbecco Commission. The twenty-five members (scientists, bioethicists, and theologians) had to evaluate the issue of stem cell research suggesting a preferred research trajectory.

Table 1. *Constitutive elements of the discursive formations on stem cell research*

	Against hESC research	Pro hESC research
Ethical formulations	Ethics of human dignity	Ethics of healing
Status of human embryo	A person from the moment of conception on the basis of a biological analysis of embryogenesis	1) The early embryo cannot be considered as a person 2) The human embryo is a person but its right to life is subordinate to the rights of fully-developed human beings 3) Because supernumerary embryos are destined to be destroyed, their exploitation for research purposes is more ethical
Image of science	1) An overwhelming science threatening moral values (rhetoric of fear) 2) Research on adult stem cells is sound science respectful of moral values	A beneficial activity promoting progress, well-being, health, and economic competitiveness (rhetoric of hope)
Role of politics	The state must assume responsibility for the protection of specific ethical values and of the dignity of human embryo	The state must promote scientific development in order to fulfill social and economic ex-pectations
Policy instruments	National or supranational parliaments	Expert advisory committees formulating policies guidelines

Source: Author's elaboration

This was a governance approach to scientific innovation which is termed the «technocratic model» of policy-making. According to this model, scientific facts, seen as objective and unproblematic, should determine proper policy[38]. This is an implicit normative assumption which sup-

[38] L. HENNEN, *Participatory Technology Assessment: A Response to Technical Modernity?*, in «Science and Public Policy», 26, 1999, 5, pp. 303-312; A. LIBERATORE - S. FUNTOWICZ, *«Democratizing» Expertise, «Expertising» Democracy: What Does This Mean, and Why Bother?*, in «Science and Public Policy», 30, 2003, 3, pp. 146-150.

presses other and rather important normative questions, such as moral and political values and democratic aspirations[39]. The dominance of expert knowledge is naturalized through routinised ways of institutional decision-making but is itself shaped by a normative worldview which evades the classic forms of democratic control. This tacit normative dimension tends to emerge dramatically when this model of policy-making deals with issues in which «fact-finding does not always occur independently of and prior to making normative judgments»[40]. This was the case of the commission appointed by minister Veronesi, which dealt with an issue where separation between facts and values (and the precedence of facts evaluation over values assessment) was simply impossible. The technocratic assumptions were evident in what Veronesi said when presenting the Commission: «What interests us is the therapeutic domain ... *The ethical debate will be considered at a later stage*» («Corriere della Sera», 21 September 2000, Italics added)

In addition to the overlapping between facts and values, this form of «sub-politicization»[41] – in which a political issue is apparently depoliticized through an expert assessment introducing, instead, political norms and decisions – in the Italian case encountered contingent problematic features related to the socio-political context. In particular, in Italy expert advisory committees are appointed directly by ministers without parliamentary control, and they are thus frequently accused of ideological partisanship. These opaque procedures of setting up annul trust in experts' assessments and infringe common sense expectations about how authoritative knowledge should be obtained; the apparent de-politicization then turns into an evident over-politicization, with a consequent lack of legitimization.

The Dulbecco Commission was immediately accused of partisanship because it overlapped with the National Bioethical Committee, which was also working on stem cell research. Since the National Bioethics Committee was seen as Catholic-oriented, Veronesi was accused of having created a counter-advisory committee closer to his secular worldview.

[39] B. WYNNE et al., *Science & Governance. Taking European Knowledge Society Seriously*, Brussels 2007

[40] *Ibidem*, p. 71

[41] U. BECK, *Risikogesellschaft. Auf dem Weg in eine andere Moderne*, Frankfurt a.M. 1986.

Moreover, the Dulbecco Commission was officially appointed on the day after the European Parliament's resolution against therapeutic cloning, which defined cloning as «contrary to public policy as adopted by the European Union» and urged «maximum political, legislative, scientific and economic efforts to be aimed at therapies that use stem cells taken from adult subjects»[42]. Veronesi was therefore accused of seeking to circumvent with a technical commission the opinion expressed by an elective assembly and thereby assert the primacy of science over ethics and politics. According to senator Alfredo Mantovano (centre-right), adopting the principle of «first the scientific aspect and then the ethical one» was to «follow the logic of national socialism» («La Stampa», 21 September 2000).

On 27 October 2000, the National Bioethics Committee released its document on stem cell research[43]. Despite paying closer attention to the ethical dimension – «the use of human stem cells raises major ethical issues which ... must be considered very carefully. This consideration must take place prior to any scientific discussion on the therapeutic potential of research in this sector»[44] – the Committee was not unanimous in its opinion on the use of hESCs. The Dulbecco Report, released on 28 December 2000, showed an analogous split on the embryo question, showing that it is impossible to separate facts and values in that particular field. Indeed, defining the therapeutic potential of the various stem cell sources requires experimentation; but experimentation should be previously permitted on ethical and political grounds. In this case, values and choices precede evaluation of the facts.

Stem cells thus demonstrated to Italian polity the difficulty of regulating technoscience in bioethical-dense fields, which give rise to «intractable controversies»[45] and in which politics acts in a social environment full

[42] European Parliament, Joint Motion for a Resolution on Human Cloning, 6 September 2000, available on web: http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+MOTION+P5-RC-2000-0710+0+DOC+XML+V0//EN

[43] COMITATO NAZIONALE PER LA BIOETICA, *Parere del Comitato Nazionale per la Bioetica sull'impiego terapeutico di cellule staminali*, Roma 2000.

[44] *Ibidem*, pp. 25-26.

[45] M. HISSCHEMÖLLER - R. HOPPE, *Coping with Intractable Controversies: The Case of Problem Structuring in Policy Design and Analysis*, in «Knowledge and Policy», 8, 1996, 4, pp. 40-60.

of uncertainties unsolvable by scientific rationality or by a sort of 'moral expertise'[46]. The cleavage within the Dulbecco Commission and the National Bioethics Committee showed clearly the limitations of technocratic approaches to policy-making in life sciences related issues. Even if the Catholic physician and bioethicist Adriano Bompiani (member of both the CNB and the Dulbecco Commission) urged the avoidance of «lay/Catholic oppositions which would be largely pointless» («Corriere della Sera», 21 September 2000), the Catholic/lay cleavage was the performative opposition which informed the entire debate. Also the SCNT technique proposed in the Dulbecco Report as a way to circumvent the embryo question – in fact the product of SCNT was framed as a «reconstructed oocyte»[47] and not as a proper embryo[48] – was an embedding mechanism which testified to the power of the Catholic position. Indeed, defining a biological entity as not properly an embryo was a way to embed social concerns and quandaries related to the embryo question in a technical discourse aimed precisely at sidestepping such concerns[49]. In this way, the apparent depoliticisation of the embryo question through an epistemic discourse was in fact an implicit acknowledgment (and a legitimization) of the power and the arguments of Catholic culture. In this sense, when the Dulbecco Report was released, Umberto Veronesi made a rather illuminating comment:

«Ours is a Catholic country. When strong opposition is raised for religious reasons, it is pointless to engage in battles of principle. It is better to find intermediate solutions, if they exist» («La Repubblica», 29 December 2000)[50].

[46] H. Gottweis, *Governing Genomics in 21st Century: Between Risk and Uncertainty*, in «New Genetics and Society, 24, 2005, 2, pp.175-194; L. Pellizzoni, *Democracy and the Governance of Uncertainty. The Case of Agricultural Gene Technology*, in «Journal of Hazardous Materials», 86, 2001, 2, pp. 205-222.

[47] Ministero della Salute, Relazione della Commissione di studio sull'utilizzo di cellule staminali per finalità terapeutiche, Roma, p. 8. available on web: http://www.salute.gov.it/imgs/C_17_bacheca_10_listaelencodocumenti_elenco1_listadocumenti_documento0_listafile_file0_linkfile.pdf

[48] On this point see G. Testa in this book.

[49] G. Testa, *Stem Cells through Stem Beliefs: The Co-production of Biotechnological Pluralism*, in «Science as Culture», 17, 2008, 4, pp. 435-448; B. Rubin, *Therapeutic Promise.*

[50] The discourse on reconstructed oocytes was depicted as a semantic ploy intended to introduce human cloning in a less controversial technical guise. Marcello Pera, philoso-

The Dulbecco Report was much debated in the mass media, but it was never discussed by Parliament, as it was released when Italy was being governed by a centre-left coalition, a highly heterogeneous political ensemble with contrasting positions on biotechnologies. The disastrous experience of the 1999 bill on assisted fertilization, when the Catholic parties of the coalition voted with the centre-right opposition, showed that bioethical issues were perilous terrain for the political equilibrium of the centre-left coalition.

V. The Law 40/2004 and the Italian way to biopolitics

In May 2001, parliamentary elections were held in Italy, and the centre-right coalition won the majority of seats. To be noted is that after the corruption scandals of the first half of the 1990s, the Italian political parties had lost much of their ideological identity and cultural legitimization. The main Catholic-oriented political party (Democrazia Cristiana) dissolved into several small parties, which deprived Catholicism and the Roman Catholic Church of their main political representative. Catholic hierarchies then began to act as a trans-party lobby in order to persuade the new political parties to adopt policies consistent with the Catholic view of society. Bioethical issues, and in particular the protection of human embryos, were among the foci of this political lobbying action. Centre-right parties were closer to Catholic stances for several reasons: ideological affinity, the need for cultural legitimization, or simply the acquisition of Catholic votes. In this period, therefore, bioethical issues became a political battleground. According to some political scientists, the Catholic/lay distinction (always present in Italian history but at the time latent) became the most important socio-political cleavage in contemporary Italy.

The centre-right coalition decided to address some bioethical issues directly, such as assisted fertilization, cloning and stem cell research.

pher of science and future President of the Senate affirmed that «they have invented the concept of the 'non-embryo'» («Corriere della Sera», 30 December 2000). Vatican spokespersons declared that in the absence of a scientifically clear demonstration that nuclear transfer does not produce embryos – Monsignor Elio Sgreccia defined SCNT as «a simple hypothesis not yet corroborated by any research published in a scientific journal» («L'Osservatore Romano», 10 January 2001) – use of the technique on human beings should not be permitted.

Stem cell research thus became part of this politicization of the Catholic/lay cleavage. As Angelo Vescovi put it: «Embryonic stem cells are left and progressive, somatic stem cells are right and conservative» («La Repubblica», 2 February 2002). In other words, allowing hESC research became a means to assert a secular concept of the state, whereas the ban on the use of embryos served to maintain a set of traditional religious values considered foundational to Italian identity and social order.

The first move in the stem cell politics was the appointment of Girolamo Sirchia, a haematologist and one of the members of the Dulbecco Commission who had opposed the use of human embryos, as Minister of Health. Sirchia set up a new commission on stem cells, but with a different task: that of deciding what kind of research projects on stem cell could be funded. Commentators noted that the members of this committee were researchers only in the field of ASCs. For the supporters of hESCs this was clearly a political decision[51], because Sirchia sought to regulate stem cell research at a sub-legislative level by means of ministerial decree, the administrative routine of an ad-hoc commission in the field of research funding.

In March 2002 parliamentary discussion began of the bill on assisted fertilization, which became Law 40/2004 on medically assisted fertilization. This law also regulates stem cell research, but it does so indirectly by simply prohibiting cloning and the use of Italian human embryos for research purposes.

Stem cell research was only a marginal issue during the parliamentary debate. To be sure, of the twenty-nine proposals then consolidated into the law, only four dealt with stem cell research, and only one provided for the liberalisation of hESC research. Other questions were the focus of heated debate in Parliament, such as access to the assisted fertilization technique, embryo or gametes donation, pre-implantation genetic diagnosis, embryo selection, and the general theme of the rights of the human embryo. In particular, political negotiation on the rights of the human embryo resulted in a normative framework in which the

[51] Renato Dulbecco, commenting on the setting up of the Sirchia Commission, stated: «if it is wanted to change direction, there is the freedom to do so. *It is only politics*», and Carlo Alberto Redi «a solely ideological choice: to privilege the study of adult stem cells precluding opportunities for research on all fronts» («Corriere della Sera», 28 November 2001).

embryo was recognized as a special subject protected by law, so that experimentation on human embryos was officially banned. The Italian law on medically assisted fertilization stated in fact:

Art. 13 – Research on human embryos.

1. Any experiment on a human embryo is prohibited.
2. Clinical and experimental research on human embryos is only permitted on condition that its pursuit concerns therapeutic and diagnostic purposes related to the health and development of the embryo itself, and if no other alternative procedure is available.
3. The following are in all cases prohibited:
   a) the production of human embryos for research or experimentation or for purposes other those stated in this law;
   b) every form of the eugenic selection of embryos and gametes ...;
   c) cloning procedures through nuclear transfer or early embryo splitting or of ectogenesis both for reproductive and research purposes;
4. the insemination of human gametes by gametes from different species and the production of hybrids and chimeras.

Although marginal, members of Parliament also discussed stem cell research during the debate. The discussion centered on the therapeutic potential of the different stem cell sources. For example, Deputy Maria Burani Procaccini (centre-right) affirmed:

> We want this law, not to halt science but to encourage it ... I speak of science, not of feats of technique. Stem cells ... serve to cure dreadful diseases, they can be harvested from the umbilical cord – this is by now known to everybody (Camera dei Deputati, session 124, 27 March 2002).

Also the supporters of hESC research, such as Senator Bettoni Brandani (centre-left), sought to embed ethical arguments in technical issues:

> The final critical point of the law in question is that, on an obscurantist principle ... it precludes the possibility of scientific research in Italy, it removes any prospect for Italian science to work, for example, on embryonic stem cells, which currently represent the most advanced frontier for curing diseases and saving the lives of millions of human beings (Senato della Repubblica, session. 462, 24 September 2003).

The embedding of the Catholic/lay cleavage in the scientific discourse on stem cell sources was definitively institutionalized during the parliamentary debate. Even if indirectly, the regulation of stem cell research entered a co-production process with national political identity. For example, Deputy Mara Cossutta (centre-left) declared:

> You perhaps do not know how different is the study of the differentiation of an umbilical stem cell from an embryo stem cell. There is a very great difference indeed. A different choice would have led to great developments in science, in the curing of diseases. I again address my so-called Catholic colleagues: frankly, in 2004, I have grown tired of talking about lay persons and Catholics ... because secularism is not a value that should distinguish us, for everybody is secular ... It is not true that ethical values are only those of Catholics (Camera dei Deputati, session 409, 20 January 2004).

Supporters of hESC research presented themselves as defenders of the secular state and promoters of a scientific progress sensitive to the needs of the sick. Opponents, such as Deputy Alessandro Cè (centre-right), saw hESCs as a threat to the (alleged) cultural and political identity of the country:

> In the recent period, in fact, we have been faced by a drift towards 'scientism': there is talk of heterologous fertilization, of mother-grandmothers, of uteruses for rent, of eugenic selection, of the use of embryos for experimental purposes and therapeutic cloning! ... This is absolutely unacceptable, and it is the result of a degeneration of the Enlightenment, of the worst part of the Enlightenment ... What has been the result? Today's world: a society without values, rampant individualism, destruction of the family, the annihilation of the identities of peoples, a relativism (which the equivalent of religious syncretism) and a scientism, that is, the belief that science can do everything and that everything that can be obtained by science is permissible (Camera dei Deputati, session. 421, 10 February 2004).

Indeed, upon first approval of the law by the Chamber of Deputies (June 2002), Girolamo Sirchia declared: «this is a victory not only for the Holy See but also for the Italian tradition, a victory for our heritage» («La Repubblica», 14 June 2002). But, apart from these examples, the discussion on stem cells took place in the frame of the embryo question, and the regulation of stem cell research emerged as a side-effect of the definition of the status of the human embryo.

This is interesting, because in the same period the discourse on stem cells changed in the newspapers. Mass media coverage was less focused on debates and more concerned with breakthroughs, experiments, and clinical trials using stem cells. It was now that the image of stem cell research as the most striking revolution in contemporary bio-medicine

was constructed. What appeared to be a visionary promise in 2000 was framed in this second period as partially fulfilled. But more careful consideration shows that a substantial amount of news stories referred to clinical protocols and therapies using ASCs. In this period, therefore, the image of ASCs changed from an ethical makeshift solution to the paramount hope for medical treatments. As Bruno Dallapiccola (geneticist and member of the Dulbecco Commission) said: «in ten years of research the progress has been astonishing » («La Repubblica», 11 July 2003). The supporters of ASCs began to criticize hESC research not only on merely ethical grounds but also because it was ineffective. According to Sirchia «it has been amply shown that the use of stem cells from an adult, and therefore taken from mature tissue, has yielded results better than those obtained with embryo stem cells» («Corriere della Sera», 26 November 2001).

Although the changing discourse on adult stem cells had little impact on the parliamentary debate, the enactment of Law 40/2004 (February 2004) was an important moment in Italian biopolitics and for stem cell research. Indeed, this law regulates stem cell research through provisions on the production and use of human embryos. It stipulates that human embryos (no more than three) may be created solely for the purpose of embryo transfer; they must not be manipulated, selected, donated or frozen for storage. The ban on donation, storage and usage in research, means that, as Metzler has pointed out, Law 40 'nationalized' Italian embryos, transforming them into 'public subjects' through the banning of the derivation of hESCs from Italian embryos and by removing them from the control of parents and physicians. In other words, Italian embryos «were embraced as public 'citizen subjects' and put under the guardianship of the state»[52]. Law 40 reflects an approach to biopolitics in which the state, faced with an opportunity to act on and manipulate human biology, has chosen to defend a set of moral values considered foundational of national identity by nationalizing and sacralising the biological entity (i.e. the human embryo) which embodies both bio-scientific opportunities and moral values[53].

[52] I. METZLER, *'Nationalizing Embryos': The Politics of Human Embryonic Stem Cell Research in Italy*, in «BioSocieties», 2, 2007, pp. 413-427, here p. 417.

[53] In this sense Law 40 is a fully biopolitical act because, through a system of norms, it regulates a set of practices, states a set of moral and ethical principles, defines subjects

Of course, the Law does not prohibit hESC research in itself; scientists may import hESC lines from abroad. But, unlike in Germany[54], the import is not regulated at legislative level; it is simply permitted as the result of a normative loophole. In fact, in April 2003 Research Minister Letizia Moratti asked the CNB for an advisory opinion on research using stem cells derived from human embryos prior to the launching of the European Union's 6th Framework Programme. The majority opinion was that even research on already derived hESCs was to be deemed unlawful[55]. On 24 April 2003, deputy minister Guido Possa, at the «Interinstitutional Seminar on Bioethics: Human Embryonic Stem Cells Research under the 6th Framework Programme for Research», transformed the CNB's advisory opinion into the official position of the Italian government. On 16 July 2004, the European Centre for the Validation of Alternative Methods (ECVAM) a European research consortium with a centre in Italy, asked the CNB if it could conduct research on hESC lines imported from foreign countries and financed with community funds on its Italian premises. The CNB, though citing its unfavourable advisory opinion, specified that law 40/2004 – the only Italian normative instrument regulating experimentation on human embryos for research purposes – did not expressly forbid research on imported hESC lines[56]. The case of the ECVAM clearly illustrates the Italian legal situation, in which hESC research ranges from being tolerated to being hampered, because public investments in stem cell research are made solely in research projects that draw on adult stem cells.

To exacerbate the situation, in the autumn of 2005 minister Moratti decided, together with the ministers of Austria, Germany, Luxembourg, Malta, Poland and Slovakia, to sign a document which called on the European institutions to exclude research projects involving human

(embryo as a person, and, through the embryo's right to be born into a family with one father and one mother, also the so-called natural family) and defines the role of politics and the state as defenders of principles and as guardians of human embryos.

[54] See A. Schwarzkopf and J. Taupitz in this book; see also S. SPERLING, *Converting Ethics into Reason: German Stem Cell Policy between Science and the Law*, in «Science as Culture», 17, 2008, 4, pp. 363-375.

[55] COMITATO NAZIONALE PER LA BIOETICA, *Parere del Comitato Nazionale per la Bioetica su ricerche utilizzanti embrioni umani e cellule staminali*, Roma 2003.

[56] COMITATO NAZIONALE PER LA BIOETICA, *Parere sull'utilizzo a fini di ricerca delle linee cellulari H1 e H9 derivanti da embrioni umani*, Roma 2004.

embryos and human embryonic stem cells from financing under the Seventh Framework Programme (FP7). Italian researchers in the field of the hESCs were thus excluded from not only national but also EC funding. Italy's signature was removed from this 'declaration of ethics' in June 2006 by the following University and Research Minister Fabio Mussi (a left-wing politician, given that in the same year the centre-left coalition won the elections). Italy's withdrawal removed the block on funding and, as a consequence, Italian researchers could obtain EU funds for research on hESC lines imported from abroad, whereas Italian public funds could be attributed only to research projects on ASCs.

Law 40/2004, as well as this *de facto* regulation at the level of research funding and administrative routines of ministerial commissions (regulation which does not follow the provisions of the law, but rather the contingent attitudes of commission members towards hESC research), are not the outcome of a shared religious feeling (depending on the diffusion of Catholicism), but of a political and cultural struggle resulting from contingent power relations in Parliament and in other governmental agencies and institutions. And, as such, this arrangement of the social order was, and continues to be, strongly contested.

VI. Engaging civil society. Stem cells, Catholicism and «laïcité»

Simultaneously with promulgation of Law 40 (February 2004) there began organized opposition against it. Political parties and patients and civic associations immediately started organizing a referendary petition to abrogate the law. Symmetrically, also those opposed to the use of human embryos started to organize in order to defend the law. The referendum campaign was a crucial event in the Italian stem cell debate because the whole population and civil society were engaged in this biopolitical struggle. During the referendum campaign, all the questions previously debated in Parliament and expert commissions (even if made public by newspapers) entered the actions and rhetorical strategies of civic and patients associations.

Stem cell research was only one of the issues debated during the referendum campaign, but it nevertheless had a certain degree of centrality: on the one hand, some patient associations focused their action on the liberalisation of stem cell research; on the other, the defenders of

Law 40 insisted on banning hESC research, considered as epitomizing the moral drift of contemporary societies. The main feature of the referendum campaign was the definitive embedding of the polarization between stem cell sources in the Catholic/lay cleavage. Indeed, the former President of the Italian Bishops Conference, Cardinal Camillo Ruini, and the Science & Life Committee (Comitato Scienza & Vita) – an association created in order to coordinate the various Catholic movements in the referendum campaign – invited citizens to abstain from voting[57]. As the Italian Constitution states that for a referendum to be valid, 50% plus one of the Italian electorate must have cast votes, an effective way to defend a law is to promote abstention by exploiting the mass of Italians who never vote. This call for abstention was seen as religious interference in political life and increased the referendum's framing in the Catholic/lay cleavage. Therefore, once again, cultural and socio-political issues were embedded in the stem cell debate. Permitting hESC research became a way to defend the *laïcité* of the state – but also a means to claim it – while the ban on embryo research was seen as a means to assert the Catholic roots of Italian society. Indeed, Camillo Ruini in his prolusion at the 54th General Meeting of the Italian Bishop Conference (30 May 2005), stated:

«We therefore want science to be at the service of the integral good of mankind ... that it does not lose sight of the value and the dignity of every human being ... There exist specific alternatives such as those instead based on stem cells obtained without suppressing embryos, and they have already yielded, unlike the others, concrete clinical results. Italian research, if adequately supported, is today extremely able to contribute to their further development»[58].

[57] See Prolusion of Cardinal Camillo Ruini at Consiglio Episcopale Permanente, Roma, 7 March 2005, available on web: http://www.chiesacattolica.it/cci_new/news_images/2005-03/07/ProlusioneCardRuini.doc. The Manifesto of Science &Life Committee (Comitato Scienza & Vita) with the call for abstention is available on web: http://www.scienzaevita.org/comitato/manifesto.php. The complete list of associations and movements costituting Science &Life Committee is available on web: http://www.scienzaevita.org/comitato/documenti/elenco_aderenti.xls; the list of 121 founders of Science & Life Committee is available on web: http://www.scienzaevita.org/comitato/membricomitato.php

[58] Prolusion of Cardinal Camillo Ruini at the 54th General Meeting of the Italian Bishop Conference, Rome, 30 May 2005, available on web: http://www.chiesacattolica.it/pls/cci_new_v3/cciv4_doc.redir_doc?id_doc=10630&id_ufficio=10&id_allegato=3751&url_rimando=/cci_new/documenti_cei/2005-05/30-4/Prol_Ruini_Assmag05.doc

On the opposite front, around one hundred scientists created the Comitato Ricerca e Salute, which issued a manifesto urging a 'yes' vote in the referendum to repeal the law, and which declared:

«We believe that the equivalence of adult stem cells with embryonic stem cells is by no means scientifically proven ... To vote 'yes' is to favour research intended to reduce the suffering of the sick ..., and it is to affirm the values of democracy, liberalism and also of religious freedom that have promoted scientific and technological progress, improving social harmony and creating conditions of well-being without precedent in the history of humanity»[59].

Indeed opponents to hESCs acted in their main arenas («Avvenire» and «Il Foglio») by repeatedly citing failures in the therapeutic application of hESCs, compared with the successes of adult stem cell procedures. For example, Angelo Vescovi stated that «there are no therapies, not even experimental ones, which involve the use of embryo stem cells ... there exist numerous life-saving therapies which ... are based on the use of adult stem cells» («Il Foglio», 22 January 2005). The most paradigmatic example of this rhetorical strategy was represented by a well-known article published by «Avvenire» on 24 May 2005 which held that

«weighed with the scales of facts and not those of propaganda, embryonic stem cells reveal an embarrassing inferiority to adult ones. In laboratories throughout the world, in fact, adult stem cells have yielded benefits – of different extents – for 58 types of disease. And the cells obtained from embryos ...? At present, their clinical utility amounts to zero».

Related to this discourse was a reframing of pluripotency according to which hESCs was hazardous and therapeutically useless. Gynaecologist Salvatore Mancuso stated that «the only stem cells which to date have yielded tangible results are those taken from the umbilical cord and from adult subjects, because they are 'reparatory' cells. Embryonic ones have instead the task of producing a tissue in its entirety, and it is extremely reduced» («Avvenire», 1 March 2005). In similar manner, biologist Augusto Pessina maintained that «stem cells in the proper sense are cells from an adult organism which, because of their intrinsic nature, after ensuring the organism's growth, intervene in physiological replacement and regeneration», while hESCs «are by definition 'totipotent', but not as an extension of the concept of stemness described above» («Avvenire», 6 June 2005). In this discourse, pluripotency, initially viewed as the main

[59] Comitato Scientifico Ricerca & Salute, Manifesto dei Cento, available on web: http://www.lucacoscioni.it/appello-degli-scienziati-i-4-s

strength of hESCs, not only lost its aura of reparatory potential but indeed became the negation of stemness. By means of this reframing, the supporters of ASCs could now appropriate moral appeals typical of the rhetoric of healing. Moreover, they could use the therapeutic ineffectiveness of hESCs to deploy ethical considerations: investing in hESCs is unethical because it means deceiving the sick.

Supporters of hESCs found it difficult to resort to the rhetoric of 'just around the corner' therapies, and they had to fall back on the less evocative rhetoric of possible future benefits. According to Kitzinger, stem cell research passes through three periods: 1) the phase of visionary promise, 2) the phase in which the promise seems to be fulfilled, and 3) a phase of setbacks and disappointments[60]. During the referendum campaign, hESCs appeared to be in phase 3, whereas ASC research, thanks to skilful propaganda, appeared to be in phase 2. The supporters of hESCs thus had to resort to arguments connected with the development of biological knowledge; as did Carlo Alberto Redi, for whom hESCs were essential for «understanding the mechanisms of stemness» («Corriere della Sera», 27 April 2005). In general, the potential of hESCs concerned the future. As Renato Dulbecco put it, «there is no comparison between what *can be done* with adult cells and what *will be done* with embryo cells» («La Stampa», 29 April 2005, emphasis added). The pro-hESC discourse therefore appeared to be a defensive strategy intended, as the biologist Giulio Cossu said, «to explore all avenues without precluding any of them» because «we still do not know enough to say which of them is better» («La Stampa», 16 May 2005). According to Elena Cattaneo, a leading expert on stem cells, «the study of embryonic stem cells [may] have great potential for the treatment of incurable diseases ... in both cases research is very distant from finding a 'cure' ... one type of research does not exclude the other. To claim that embryo cells are useless is irresponsible; one should have the courage to say 'I do not use them because it is against my principles'» («La Stampa», 28 May 2005). But possible future benefits have less evocative power than the claims of (alleged) actual therapies.

[60] J. KITZINGER, *Questioning Hype, Rescuing Hope? The Hwang Stem Cell Scandal and the Reassertion of Hopeful Horizons*, in «Science as Culture», 17, 2008, 4, pp. 417-434, here p. 419.

When the polls closed (13 June 2005), the turnout for the referendum was only 25.9%, very distant from the *quorum* required by the Italian Constitution. The outcome of the referendum definitively confirmed the stabilization of a social order, and because it involved Italian citizens directly it was able to define Italian society as well. According to Cammillo Ruini, the outcome was indicative of «the maturity of Italians, who refused to pronounce on technical and complex issues, who love life and distrust a science which wants to manipulate life» (Radio Vaticana, 14 June 2005). Of course, the interpretations given by the supporters of abrogation were very different. For some of them, the outcome was the effect of a general lack of interest in bioethical issues, not of deliberate abstention. But for others, the low turnout testified to the failure of a secular culture, even if in Italy referenda nearly always fail in any case.

As in the case of the parliamentary process, stabilization of the social order which emerged from the referendum was the victory of Catholicism not in the sense of a shared cultural and religious feeling, but rather in that of the ability of Catholic actors (members of the clergy, associations, and so on) to impose their view of the social order in crucial regulatory arenas by exploiting scientific discourse, moral appeal, power relations, and positional advantage (i.e. the frequent tendency of Italians not to turn out to vote). In co-production terms, we may say that the victors in the struggle imposed a social order in which hESC research was banned and Catholic ethics (re)affirmed their foundational value for Italian identity.

VII. Concluding remarks. A never-ending debate

The regulation of stem cell research in Italy can therefore be viewed as a classic case of co-production. The actors involved in decisions concerning what type of research to permit have also discussed issues such as the national identity (secular or Catholic), the role of science and the Church in public life, the type of ethics that should inform political choices, and the political and normative instruments that should regulate bioethically complex technoscientific questions. These views of society have thus been incorporated into research trajectories to such an extent that they have disappeared by camouflaging themselves behind

the technical discourse on therapeutic effectiveness. The regulation of research on stem cells has therefore become a battleground on which different views of the social order have confronted each other, and the outcome of which has been the establishment of a given order. But on what has this outcome depended?

As I have tried to suggest, it is not the logical consequence of the spread of religiosity among Italians, but rather of the capacity of the actors engaged in the debate to mobilize resources, to position themselves in decision-making arenas, and to exploit the structural characteristics of the Italian political system. In parliament, the prohibition of embryo research has derived to a large extent from the interest of certain political parties in positioning themselves on one side of the Catholic/lay cleavage in order to benefit from the cultural legitimation which the Catholic Church can bestow in regard to civil society. During the referendum campaign, instead, the opponents of hESC research made use of the tendency of many Italians not to vote in referenda (that is, they exploited the positional advantage of abstention, given the *quorum* rule). They also skilfully utilized the technical discourse on therapeutic effectiveness to neutralize the promises of hESCs and magnify those of ASCs. For their part, the supporters of hESCs instead found themselves in an unfavourable position in the political and institutional system, and the difficulties of hESCs in moving «from bench to bedside»[61] diminished the evocative power of the therapeutic promises. The result was the victory of the Catholics but not of Catholicism, even though framing the controversy in terms of the Catholic/lay cleavage enabled those actors to interpret the outcome as a triumph of Catholicism in

[61] On this general point see S.P. WAINWRIGHT et al., *From Bench to Bedside? Biomedical Scientists' Expectations of Stem Cell Science as a Future Therapy for Diabetes*, in «Social Science and Medicine», 63, 2006, pp. 2052-2064; S.P. WAINWRIGHT et al., *Remaking the Body? Scientists' Genetic Discourses and Practices as Examples of Changing Expectations on Embryonic Stem Cell Therapy for Diabetes*, in «New Genetics and Society», 26, 2007, pp. 251-268. On the general theme of the negotiation among different actors' expectations in stem cell research see S.P. WAINWRIGHT - M. MICHAEL - C. WILLIAMS, *Shifting Paradigms? Reflections on Regenerative Medicine, Embryonic Stem Cells and Pharmaceuticals*, in «Sociology of Health & Illness», 30, 2009, 6, pp. 959-974; see also L. ERIKSSON - N. STEPHENS - A. WEBSTER, *Introduction. Stem cell places, spaces and flow*, in «New Genetics and Society», 27, 2008, 2, pp. 83-85. On the theme of constructing narratives and stories of hope and promise in stem cell research see I. GEESINK - B. PRAINSACK - S. FRANKLIN, *Stem Cell Stories 1998-2008*, in «Science as Culture», 17, 2008, 1, pp. 1-11.

Italian public life. The positioning of the centre-right political parties was thus strengthened, while the opponents of hESCs acquired a favourable position in power relations and access to decision-making centres.

Further confirmation of this interpretation is provided by the manner in which research on imported hESC lines is still regulated in Italy. Although not forbidden by law, it is hindered *de facto* by a lack of government funding. Despite protests in the mass media, questions in parliament and recourse to the administrative courts, state funding policies systematically exclude research on hESCs. This is because the heads of the administrative bodies responsible for funding are experts in ASCs who have been selected by centre-right governments. Positioning oneself in the decision-making nodes crucial for determining the type of research to conduct therefore becomes the means to maintain the social order embedded in one type of research trajectory. These research policy choices, moreover, are justified by resorting to technical discourses on the therapeutic potential of stem cell research which legitimate the political choices concealing the ethical positions and the visions of society that inform them. Nevertheless, because of the co-production relationship, research policies in fact stabilize the social order founded upon those positions and visions.

Consequently, the configuration of stem cell research in Italy depends less on structural variables such as culture and religious belief than on the capacity of important social actors to exploit power relations and political contingencies within the institutional system. It also depends on the ability to make tactical use of scientific discourses (and their changes) on the clinical potential of the different sources of stem cells. It is therefore difficult to predict the future evolution of the regulation of stem cell research in Italy, because it is embroiled in a struggle to stabilize the social order, it will depend on the local and temporary results of that struggle amid political contingencies and fluctuating power relations.

Stem Cells and the Structuring of the Italian Biopolity

by *Giuseppe Testa**

I. Introduction

In this work I analyse three salient moments in the Italian history of stem cells as objects of at once scientific inquiry and political contestation. They are: (1) the proceedings of the Dulbecco Commission on stem cells in 2000; (2) the referendum campaign conducted in 2005 to repeal the law forbidding human embryonic stem cell (hESC) derivation, and (3) a recent challenge brought by Italian scientists against the government's decision to exclude hESC from funding. The reason for selecting these developments is that they embody the three public encounters between the Italian polity and stem cells, and thus allow us to probe the resources, both scientific and political, with which Italy has grappled with this technoscientific innovation.

In the history of post-war Italy, stem cell research, and specifically embryonic stem cell research, has been undoubtedly one of the most hotly debated scientific issues. Importantly, as in many other countries, embryonic stem cells have also become one of the most enduringly contested objects, in the sense that, since their appearance on the public scene in 1998, political closure on the practices of their existence has been difficult to achieve, fragile and, very often, only transient. The history of stem cell science and stem cell politics is therefore already rich and dense, offering a protracted series of encounters between the scientific and the social aspects of their development, between the making – and unmaking – of new knowledge in laboratories and the production of norms that inspired, accommodated or simply resisted this wave of technological change. My question is thus how Italy came to know stem cells and how it decided on their moral and political

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status, through which epistemological and political resources, and with what consequences for the structure of the Italian biopolity. To this end, I will apply the innovative interpretive framework of civic epistemology, recently developed by Sheila Jasanoff in her comparative analysis of life science policy in the US, the UK and Germany. In the original formulation, civic epistemologies refer to the «institutionalized practices by which members of a given society test and deploy knowledge claims used as a basis for making collective choices»[1]. The core of this notion is the collective act of knowing. The emphasis is on how publics come to know things and to decide what is worth knowing in the first place. It is «epistemology» because it deals with the foundations of knowledge claims, with the standards of evidence and the notions of objectivity that underlie the making of facts. But it is «civic epistemology» in that it probes how those knowledge claims are licensed in the public sphere; and how citizens and the institutions that represent them grapple with notions of evidence and objectivity to arrive at a shared understanding of technoscientific developments.

II. The Dulbecco Commission and the framing of clones

In 2000, in the wake of the announcement of Dolly the sheep in 1997[2] and the first isolation of hESC by James Thomson in 1998[3], the Italian government appointed an expert body to advise on stem cells and cloning and propose policy recommendations. The commission was headed by Nobel prize-winner Renato Dulbecco and included twenty-six members: seventeen life scientists and physicians, four philosophers, three theologians (including a cardinal), one judge and one politician. In appointing this expert body, health minister Veronesi asked the commission to address four aspects of the emerging stem cell science: the medical potential of stem cells; the expected time frame within which this potential could be achieved; the type of diseases that could be treated with stem cells; and what source of stem cells (embryonic,

[1] S. Jasanoff, *Designs on Nature*, Princeton NJ, 2005, pp. 255-271.

[2] I. Wilmut et al., *Viable Offsrping Derived from Fetal and Adult Mammalian Cells*, in «Nature», 285, 1997, p. 810.

[3] J.A. Thomson, *Embryonic Stem Cell Lines Derived from Human Blastocysts*, in «Science», 282, 1998, p. 1145.

adult, foetal, or cord blood) was scientifically and ethically preferable. A detailed analysis of the commission's work has been recently published[4]. Hence, in what follows, I will briefly recount only the salient outcome of the commission proceedings in regard to its relevance for our discussion of scientific expertise in the making of the Italian civic epistemology. Briefly, in most aspects of its policy recommendations, the commission followed the lay/catholic divide and *de facto* upheld it as an apparently foundational feature of the Italian biopolity. Thus, the commission split over the permissibility of hESC derivation from in vitro fertilization (IVF) of surplus embryos, with a 'lay' majority endorsing it and a 'catholic' minority opposed to it. The unique contribution of the commission, however, and its most explicit epistemological engagement, was its unanimous endorsement of somatic cell nuclear transfer (SCNT). This technique was deemed exempt from ethical problems because its product was framed not as an embryo but rather as an extension of the prospective patient's body. In the commission's own wording,

«The term 'therapeutic cloning' to indicate SCNT is clearly inappropriate. In fact, an enucleated oocyte reconstructed with an adult somatic cell nucleus cannot be considered a classic zygote, because it does not derive from the union of two gametes. This is proven by the fact that such a reconstructed oocyte does not develop spontaneously into an embryo, and this happens only following artificial stimulations that force it to develop into a blastocyst. Only few of these blastocysts possess the effective capacity to form an embryo, and hence a foetus, once transferred into the uterus ... Finally, the oocyte reconstructed with a somatic cell nucleus is much more similar to a potential form of asexual cellular expansion of the patient, in analogy to what is currently practiced when skin biopsies are amplified in vitro to produce artificial skin for the treatment of major burns»[5].

This was a unique reframing of cloning as a process that could expand the potential of a person's own skin cells while stopping short of intersecting the trajectory of nascent human life. Today, in the mature age of induced pluripotent stem cells (iPSC) that have indeed expanded the potential of any skin cells towards virtually any bodily lineage[6], the vision advanced by the commission seems almost prophetic, though at the time

[4] G. TESTA, *More than Just a Nucleus. Cloning and the Alignment of Scientific and Political Rationalities*, in S. JASANOFF (ed.), *Reframing Rights. Constitutional Implications of Technological Change*, Cambridge MA 2011, pp. 85-104.

[5] *Ibidem.*

[6] S. YAMANAKA, *Strategies and New Developments in the Generation of Patient-specific Pluripotent Stem Cells*, in «Cell Stem Cell», 1, 2007, p. 39.

its lack of experimental evidence was heavily criticized, especially in the catholic-oriented press[7]. For the purpose of our analysis here, however, what emerges is a salient example of civic epistemology, in which the crafting of political compromise goes hand in hand with an ontological exercise in kind-making that orders novel experimental practices and new life forms along the reassuring natural versus artificial divide.

III. The referendum on assisted reproduction and human embryonic stem cells

The epistemological creativity of the Dulbecco Commission was not matched by legislation, and in 2004 the centre-right majority passed a new law, Law no. 40, that imposed severe restrictions on assisted reproduction and on human embryonic stem cell (hESC) research. The Law was enacted amidst heated controversy, and in 2005 Italy held a referendum to repeal it. Law 40 declared its aim at the outset: the protection of all interested parties, including the zygote, which was thus officially recognized for the first time as a bearer of legal rights. The following articles clarified that in vitro fertilization (IVF) was only permissible for heterosexual couples, in which both members were alive and of fertile age. Heterologous fertilisation, homosexual parenthood, posthumous fatherhood, postmenopausal motherhood and surrogacy were all forbidden. The production of supernumerary embryos was also prevented with the obligation that in each round of IVF all embryos produced should also be implanted. Preimplantation genetic diagnosis was also excluded. Finally, Law 40 also forbade the derivation of new embryonic stem cell lines from human embryos. The possibility to use for research existing hESC lines derived elsewhere was instead left unaffected (but we shall see how precisely this research option would trigger the most recent biopolitical controversy). In short, Law 40 framed assisted reproduction as a prosthetic extension of natural reproduction that became legal only insofar as it made possible what 'naturally' could – and by implication should – have been possible. The law ignited heated controversies from the very beginning, and trig-

[7] G. Testa, *More Than Just a Nucleus. Cloning and the Alignment of Scientific and Political Rationalities*, in S. Jasanoff (ed.), *Reframing Rights. Constitutional Implications of Technological Change.*

gered an intense campaign to gather the minimum number of 500,000 signatures required in Italy in order to propose a referendum on repeal of an existing law. The campaign was fuelled by the Radical Party, a small party that had very often used the referendum tool in previous decades and had been instrumental in setting a successful progressive agenda on bioethical issues and civil rights, including abortion. The referendum was eventually approved by the Constitutional Court and on 12 June 2005 Italians were called upon to vote «yes» or «no» on four questions, three of which concerned assisted reproduction and one concerned hESC research. «Yes» would have cancelled Law 40 and bound Parliament to enact new legislation coherent with the popular vote, hence giving a green light also for hESC research. «No» would instead have left Law 40 in force.

A detailed analysis of Law 40 would be beyond the scope of this discussion, and here I will focus instead on the part of the referendum campaign that dealt with hESC as an obvious articulation of the Italian civic epistemology on this topic. For one thing, Italians were called upon to decide whether or not they wanted to acquire knowledge on and through hESC. In turn, this decision assumed the formation of a shared understanding of what these new scientific objects were, of how they intersected with the trajectory of nascent human life and of their relative importance in the edifice of biological knowledge and its possible medical applications. It was thus a thoroughly epistemological instance because it concerned the ontology of new objects, their relationship to more familiar though equally disputed ones (embryos, aborted fetuses, contraceptives etc.) and the decision about whether or not to purse knowledge on them and with them. And it was evidently civic in that an entire nation was called upon to decide on this ontological and normative issue. A rich comparative analysis of life science policy in the US, Germany and the UK has shown that civic epistemologies are to a large extent culturally specific[8]. Each of the countries examined reacted to the apparently homogenizing thrust of technoscientific innovation with novelty-ordering practices that resonated with long-standing and often culturally specific notions of what counts as scientific knowledge and of who is entitled to interpret it or speak on its behalf. Therefore the relative place of scientific expertise in a given country, the way in

[8] S. JASANOFF, *Designs on Nature. Science and Democracy in Europe and the United States*, Princeton NJ 2005, pp. 255-271.

which it is recognized, presented to the public and mobilized by the political power to ground decisions, is a central feature of any civic epistemology. Accordingly, I will examine in what follows the unfolding of stem cell scientific expertise during the Referendum campaign of 2005.

1. *The construction of a divided scientific community*

First to be noted is that the referendum campaign presented a bitterly divided scientific community to the Italian public. This was in stark contrast with the features of the hESC debate in most other Western countries. In Germany and the UK, for example, the scientific community stood relatively homogeneously in favour of hESC research, and the main frictions were between the scientific community and the patients' advocacy groups, on the one hand, and various other actors on the other, including the Catholic Church, sections of conservative parties, and historical anti-abortion advocacy groups. There were of course exceptions, and an Italy-US comparison conducted in the next section will show how in the US two scientists opposing hESC have recently become prominent and successful actors in this controversy. But by and large communities of scientists have acted relatively homogeneously in favour of hESC throughout Western countries.

In Italy the situation was different; or, put better, what the scientific community as a whole stood for was articulated in a drastically different manner. Throughout the Italian media, in the press and even more so on television, discussions to inform the public on the impending referendum followed a rather homogeneous format: two scientists were usually invited to present their views, one in favour of hESC research, the other opposing it. From the staging itself of the televised debates (relatively few to start with), including the way in which the various anchormen introduced scientists and guided the debate, the impression given was clearly that of a symmetrically split scientific community, of two competing views on the merits of hESC that were on an equal footing not only in their ambition to convince Italian citizens, but also in their credibility at the level of the international scientific community. There was little if any trace of the fact that the overwhelming majority of scientists worldwide did indeed trust hESC as a highly promising new field of inquiry and that dissenting voices amounted to a small minority, often inspired by a self-proclaimed, fully legitimate but certainly very

clear ethical agenda that considered hESC research akin to murder. But why was the construction of a divided scientific community, especially in the media, so important? The reason, as I describe below, lies in the specific kind of discourse within which scientific expertise was deployed.

2. *The primacy of facts*

In theory, the peculiar rendering of scientific expertise outlined above might be thought have relatively little significance. After all, one might expect that in a referendum so obviously about values, where the voter had to decide whether an in vitro fertilized embryo should be treated like a full fledged person or could be destroyed to generate potentially useful cells, what stem cell experts thought was *prima facie* of little relevance. And therefore that also the way in which their expertise was presented was of marginal importance. If the question was primarily normative (do we need to respect human in vitro embryos or can we use them?), all considerations regarding the potential value of hESC for biomedicine could have, at most, a secondary role, possibly as a second tier balancing the value of the embryo against the potential benefit derived from hESC.

Yet despite its value-laden premises, the Referendum campaign largely skirted around an explicit value discourse and sailed instead on the apparently safer waters of objective scientific knowledge. There was relatively little room for the soul and disproportionately more space for the genome. Although, as we shall see, the Catholic Church was the most effective actor in the campaign, very seldom did its representatives defend in public discussions the notion that human life was sacred or that the in vitro embryo had a soul just like every other human. More often than not they resorted instead to scientific claims in order to support their position against embryo destruction and hESC research. The embryo is one of us, so the argument often ran, because it has a distinctive genome, not because it has a soul. And in fact the very notion of life's beginning was grounded in the acquisition of a distinctive genome at fertilization, rehearsing the widespread conflation between human dignity and genomic uniqueness that has pervaded the human embryo debate worldwide. And hESC were not just morally objectionable, they were indeed useless, according to the scientists who campaigned for the «No» vote. Against this backdrop, it is then clear

why the manner in which scientific expertise is mobilized is crucial. If the fight proclaims itself to be primarily about 'facts', the way in which expertise on the facts is presented is bound to be of key importance.

But what were the 'facts' on which the Italian public was called to vote, and who was speaking on their behalf? The two chief facts that defined the referendum controversy on hESC had both to do with the dichotomy between embryonic and adult stem cells. Indeed, I would argue that the very fact that this dichotomy came into being as a publicly salient distinction was itself the main epistemological aspect in the civic epistemology we are analyzing. Clearly, this dichotomy was not invented in Italy – and in fact it pervaded the embryonic stem cell debate worldwide – but its uptake in Italy appears, as we shall see, to have been highly distinctive.

The first 'fact' was the ability of adult stem cells to acquire features typical of tissues other than those from which they were originally sourced. It was at the core an epistemological controversy because it dealt with the standards of evidence necessary to make claims about stem cells. For a few years, roughly from 1999 to 2003, the unexpected ability of adult stem cells to transdifferentiate into a variety of other cell types gained enormous prominence in the leading scientific journals. A new scientific entity was born, and it very soon became also an object with acute political meaning, the transdifferentiating adult stem cell. We can trace the beginning of this scientific and political wave to a prominent article on the ability of brain cells to generate blood published by Angelo Vescovi, an Italian scientist who was to play a crucial role in the referendum campaign analyzed here[9]. Given the heated political controversy on hESC, the unexpected abilities of adult stem cells spurred more than just scientific curiosity, and they were soon adduced by hESC opponents as evidence that the regenerative hopes triggered by hESC could be fulfilled also by adult stem cells, thus avoiding any moral problem. It suddenly seemed that any cell type had the spontaneous ability to generate virtually all other cell types, and there is no question that the political saliency of the hESC controversy contributed greatly to the apparent ease and speed with which these unexpected findings were welcomed into the leading life science journals. Eventu-

[9] C.R.R. Bjornson et. al., *Turning Brain into Blood: A Hematopoietic Fate Adopted by Adult Neural Stem Cells in vivo*, in «Science», 283, 1999, p. 534.

ally, however, controversies erupted that called some of the landmark papers on transdifferentiation into question[10]. The disputes concerned two core epistemological aspects: the standards of evidence necessary to warrant the claim that cells actually changed fate; and the physiological relevance of anecdotal observations of phenomena that almost invariably appeared to be exceedingly rare. A thorough analysis of these controversies would clearly be beyond our focus here, and for our purposes it suffices to recall that the reports on the transdifferentiation of adult cells were quickly adopted, in most countries, by hESC opponents as crucial evidence that hESC were, after all, entirely unnecessary. The critical point for our analysis, however, is that in most countries this position, with few exceptions, was not embraced by leading scientists, let alone by significant fractions of the scientific community. Any Western country, for obvious historical reasons, had a broad spectrum of scientists working on either adult or embryonic stem cells, and sometimes on both, viewing them as experimental systems with complementary strengths. But very few scientists working on adult stem cells seemed prepared to argue that the very existence of their research made hESC unnecessary. Most scientists instead lobbied for a general endorsement of the stem cell field as such, regardless of the specific type of stem cell that each preferred to study. Indeed, the launch in 2002 of the International Society for Stem Cell Research (ISSCR) set the international seal on the reshaping of several strands of biological research into the newly defined discipline of stem cell science.

The second 'fact' is closely connected to the first. It concerned the potential utility of stem cells in clinical practice. In 2005, David Prentice, an American physician actively involved in research ethics and policy, published a report that was to be hugely influential in the hESC controversy. The so-called *Prentice Report* announced that 65 diseases had already been cured with adult stem cells, whereas no disease had yet been treated with hESC. The stark comparison was emphasized in table format: on the left of the table, under the heading «adult stem cells», a long list of serious conditions; on the right, under the heading «embryonic stem cells», a most telling void. This appraisal of the current status of stem cell science was immediately and widely criticised on two main grounds. First, it entailed a patently unfair comparison

[10] M. RAFF, *Adult Stem Cell Plasticity: Fact or Artifact?*, in «Annual reviews in cell and developmental biology», 19, 2003, p. 1.

between two 'technologies' – adult and embryonic stem cell culture – with histories of very different durations. It seemed at best implausible, in 2005, to compare the clinical utility of hESC, first derived in 1998, with that, for example, of hematopoietic stem cells, whose use in bone marrow transplants dated back some decades. Second, the list of 65 diseases cured with adult stem cells prompted a fundamental dispute about the definition itself of 'cure'. In the columns of «Science»[11] and the «New England Journal of Medicine»[12], groups of scientists analyzed the claims of the Prentice Report and exposed the ill-defined criteria that had been used to define the 65 diseases as «cured». The extent of the controversy became even clearer when Prentice himself replied, again in Science, that the 'cures' he described were not necessarily meant to be taken as certified medical treatments fully approved by the Food and Drug Administration (FDA); rather, they included a variety of treatments that had only been shown to «help», «aid» or «improve» the condition of patients. We are thus at the heart of the controversy about what should count as reliable knowledge in the public domain and what is needed to certify it. In Italy however, Prentice's list was quickly adopted and became a critical 'fact' in the articulation of the referendum campaign. Thus, on 24 May 2005, the daily newspaper of the Italian Bishops Conference (CEI) «Avvenire» published an article entitled *Adult 58, Embryonic 0: No Game between Stem Cells (Adulte 58, embrionali 0: tra staminali non c'è partita*, G.T.)[13]. In a country polarized around soccer rivalries, the title slyly used the sporting metaphor to turn the plurality of stem cell research options into a battle won by adult stem cells beyond any reasonable doubt.

But if these were the salient 'facts' on which the referendum campaign was fought, we can now return to the role played by Italian scientists, because these 'facts' could obviously become such only through the legitimizing stance of publicly recognized experts. And whilst Dr. David Prentice had managed to compile a 'factual' list from a diverse mixture

[11] S. Smith - W. Neaves - S. Teitelbaum, *Adult Stem Cell Treatments for Diseases?*, in «Science», 315, 2006, p. 439.

[12] R.S. Schwartz, *The Politics and Promise of Stem Cell Research*, in «New England Journal of Medicine», 355, 2006, p. 1189.

[13] A. Massarenti, *Staminalia. Le cellule «etiche» e i nemici della scienza*, Parma 2008, p. 20.

of actual treatments and wishful hopes, also Italian scientists played a key role in seemingly letting the 'facts' speak for themselves.

3. *The mobilisation of scientific expertise and the «Science and Life» Association (Comitato Scienza e Vita)*

A productive way to analyse the role played by experts in technoscientific debates is to focus not only on what kind of knowledge they communicate but also on the relationship they establish with the various political actors and stakeholders that shape a civic epistemology. In this regard, we find scientists aligned on either side of the divide during the referendum campaign, although – in contrast to the media representation of this divide – it was only a minority, though a very vocal one, that explicitly campaigned against hESC. And on both sides we find scientists allied with influential political actors who shaped the discourse agenda of the campaign. The prime advocate of the freedom to research on hESC was the Luca Coscioni Association, recently well-described as «a collective of politicians, physicians, scientists, infertile couples and patients suffering from chronic genetic diseases»[14]. The two most prominent scientists to campaign in favor of hESC, and who acted as key consultants for the Luca Coscioni Association, were Giulio Cossu and Elena Cattaneo, two leading scholars active, respectively, in the fields of muscular and neuronal degenerative diseases. Interestingly, however, also patients themselves were able to assert, through the Luca Coscioni Association, their own special form of expertise resulting from their first-hand experience of the sick body. Indeed, Luca Coscioni himself, the founder of the association who suffered from amyotrophic lateral sclerosis and was member of the above-mentioned Radical Party, defined himself as an expert on «bio-ethics through [his] own skin»[15]. Hence, the alliance of leading stem cell scientists with this political collective of patients started to import into the Italian polity a well-rehearsed process that had been pioneered in the United States and the UK: the evolution of patients' organizations from pressure lobbies into key research funders, followed by the public recognition of their

[14] I. METZLER, *Between Church and State: Stem Cells, Embryos and Citizens in Italian Politics*, in S. JASANOFF (ed.) *Reframing Rights*, pp. 105-124.

[15] L. COSCIONI, *Il maratoneta. Dal caso pietoso a caso pericoloso. Storia di una battaglia di libertà*, Viterbo 2003, p. 122, as cited in I. METZLER, *Between Church and State.*

role in knowledge production through the co-authorship of seminal human genetics publications[16].

What is instead more specifically Italian is the alliance between scientists and political actors that shaped the front opposed to hESC research. In fact, whilst in several Western countries, as mentioned above, individual scientists have occasionally allied with conservative parties and/or the religious right in opposing hESC research, to my knowledge Italy provides the first example of a thoroughly coordinated effort in which prominent scientists co-founded with the apex of the Catholic Church an association to oppose the referendum and secure the legal ban on hESC research. Furthermore, after this association, called «Comitato Scienza e Vita» (Science and Life Association), won the referendum, it went on to become a central actor in most bioethical debates in Italy. This is perhaps the strongest reason why the referendum campaign, through the birth of the Science and Life Association, can be recognized as having played a structuring and enduring role in the Italian biopolity. The association was highly supported by the head of the Italian Bishops Conference (CEI), Camillo Ruini, and constituted a powerful alliance between the Catholic Church and a group of scientists, some of whom were already prominent in the Italian context and who acquired great visibility during the referendum campaign. As the Association's name itself implies, it was careful from the outset to forestall the perception that it was in any way anti-scientific or opposed to scientific progress. On the contrary, the stamp of scientific credibility was actively sought, and the recruitment of influential Italian scientists as testimonials was instrumental to articulate the associations' ambitions well beyond the traditional Catholic audience.

Through the Science and Life Association, Camillo Ruini masterminded the campaign with shrewd tactics made possible by the peculiarities of the Italian law regulating referendums. Far from being a neutral polling of public opinion, in Italy a referendum is a tool of deliberation in which the interrogation of voters' views is substantially constrained and shaped by government action. For one thing, a referendum in Italy can only repeal laws, a first indication of the lawmakers' desire to tame the innovative potential of direct participation. But even more

[16] H. Nowotny - G. Testa, *Naked Genes. Reinventing the Human in the Molecular Age*, Cambridge MA 2011, p. 38.

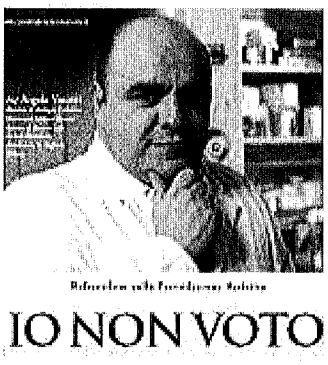
importantly, referendums are valid only when at least 50% plus one of the potential voters effectively vote (the so called *quorum).* The immediate consequence has been the creation of a system with three voting options that all have effective force: voting «yes», voting «no» and «abstention». In turn, this creates a fundamental bias and asymmetry in favour of the maintenance of the *status quo.* In fact, even in national political elections – the moment of greatest democratic participation – there is a relatively constant abstention rate that usually amounts to about 25%. This is usually higher in less participated occasions, such as European elections or, indeed, referendums. In a system that prizes the decision not to vote as a negative ballot, it is clear that this percentage of 'chronic' non-voters is automatically recruited to the front opposing the referendum question, which therefore inevitably starts with a major advantage over the front promoting the referendum.

This feature of Italian referendums was effectively exploited by Bishop Ruini when he decided that the Science and Life Association would campaign not for a «No» vote but for a non-vote. In this way, he secured upfront for his side a tacit alliance with the fraction of chronic non-voters. The massive campaign for the non-vote also brought a radical alteration to the secrecy of voting. Contrary to the decision to vote «yes» or «no», the decision of whether or not to go to the polls was in fact potentially much more easily influenced and controlled, open as it was to public scrutiny, especially in small rural villages where the Catholic campaign was more likely to exert a strong hold.

But the most interesting aspect of the Science and Life Association's campaign, at least for our biopolitical analysis, concerns its discursive strategies more than its electoral tactics. The association mounted a vigorous campaign that combined an appeal to scientific authority with the denial that hESC and assisted reproduction could be seen as political issues. Besides its already telling presence in the name of the association, Science came in the guise of the prominent scientists who became regular guests on television talk-shows dealing with the imminent referendum. But even more telling, through the evocative power of images, was the massive poster campaign. Two prominent scientists, Angelo Vescovi and Bruno Dallapiccola, who were also among the founders of the Association, were depicted in their white coats next to a concise description of their professional credentials and above the heading «I'm not voting» (see fig. 1). Even prominent scientists

were not going to vote: this was the clear and highly effective message conveyed by the campaign.

Figure 1. *National referendum campaign poster*



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But equally interesting, if not more so, was the part of the campaign devoted to denying that it was even possible, let alone desirable, to vote on such matters. One of the most frequently displayed posters during the campaign, arguably the landmark image of the Science and Life Association, featured two adult hands holding a baby's head, and the prominent heading «Life cannot be put to the vote» (see fig. 2).

Figure 2. *National referendum campaign poster*

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This, then, was the core message of the entire campaign: the denial that this was a political matter on which citizens could have their legitimate say. It was instead a set of questions that were, by their definition and framing, beyond politics and therefore better left to the watchful care of the two sets of experts – the clerics and the scientists – who were joining forces, for the first time, in such a public and organised manner.

IV. Defining research and the scope of its freedom: the legal suit over hESC

I now turn to the most recent and salient development in the history of Italian stem cell science. It concerns the legal fight initiated by three Italian researchers who disputed a funding call for stem cell research issued by the Italian Health Ministry (Ministero della Salute). This case is particularly relevant to the theme of this book insofar as it articulates, from the specific vantage point of stem cell science, fundamental contestations over the nature of the research enterprise in the Italian polity. In particular, at stake is the respective role that scientists and policymakers ascribe to each other in the governance of the collective production of knowledge. In order to chart this territory, I will apply a comparative methodology and juxtapose this latest development in Italian stem cell politics with a most recent and oddly symmetrical one in the US that revolves around the very same issues. Indeed, what emerges from this comparative analysis is an ontological reframing of the meaning of research, and of the limits to its freedom, whose implications transcend the territorial borders of Italy and the US.

1. *Italian stem cells: the remains of scientific freedom*

In June 2008 the newly-appointed Italian Health Minister Ferruccio Fazio appointed an expert committee to draft the call for applications regarding an € 8-million fund on stem cell research. The committee consisted of five scientists, and the text of the call was made public on 26 February 2009. After declaring stem cell research a strategic resource for pursuit of the priorities set for the National Health Service (Sistema Sanitario Nazionale), the call went on to define the two broad topics of the call: 1) stem cell biology as a basis for therapeutic applications and 2) stem cells as biomarkers and therapeutic targets. Surprisingly,

despite the broad framing of stem cell biology and the lack of disease-specific restrictions, the call explicitly excluded projects using human embryonic stem cells (hESC). This was unexpected on two grounds. First, the Law 40, as we saw in the first section, did not forbid research with existing lines of hESC, but only the derivation of new lines from embryos. Second, it immediately became a mystery how this exclusion had been inserted in the call, since Giulio Cossu, the prominent stem cell biologist mentioned above and one of the five members of the committee, declared that the sentence excluding hESC had not been agreed upon in the committee and was not present in the text which the committee had licensed. To date, it is still unclear how and when such a dramatic intervention in the call text came about. Before becoming public, in fact, the call had to be approved by the so-called State-Regions Conference, an assembly comprising representatives from the twenty Italian regions, as well as from the Ministry that allocates the national health budget. In interviews with the press, Minister Fazio declared that the sentence had been added by the regional representatives; but the representative from Tuscany, Enrico Rossi, denied this and claimed that the State-Regions Conference had neither discussed nor requested any changes to the stem cell call.

The exclusion of hESC from this first major public investment in stem cells provoked an outcry among Italian researchers. In particular, on 24 June 2009, one month before the deadline set by the call for the submission of proposals, three scientists, Elena Cattaneo, Elisabetta Cerbai and Silvia Garagna, filed an appeal with the administrative court in Rome. The scientists claimed that the exclusion of a legal research instrument (such as hESC) violated the freedom of research protected by the Italian constitution and amounted to an abuse of power by the Italian government[17]. In Cerbai's own words «Our appeal is a matter of principle. Politicians should decide strategic objectives and leave scientists to choose how best to achieve those objectives»[18].

As we see, the controversy was from the outset about the legitimacy of the political shaping of research directions. Once a government has identified the strategic fields of science that it wants to promote (in

[17] E. Cattaneo - E. Cerbai - S. Garagna, *Italy's Stem Cell Challenge Gaining Momentum*, in «Nature», 463, 2010, p. 729.

[18] A. Abbott, *Italians Sue over Stem Cells*, in «Nature», 460, 2009, p. 19.

this case stem cells), is it also authorised to detail which research tools should be used, or ought this decision to be left solely to scientists?

Just a few days before the call deadline, Rome's administrative court struck down the appeal on grounds that reframed the notion itself of scientific freedom. For the court, the three scientists did not have legal standing to file the appeal because this could be initiated only by their institutions as such. In the court's framing there was thus no direct relationship between individual researchers and the public institutions that were supposed to fund their work. The relationship existed only between the Ministry and the research institutions, with rather obvious restrictive implications for the possibility that researchers might ever be able to question any governmental decision. For this would require the individual researcher to persuade the institution to sue the government on his/her behalf. The three scientists maintained that this clause violated the freedom of research because the right to freedom of research is enshrined in the constitution as a right of the individual[19]. For what remains of the right to freedom of research if, in the fight for its protection, individual scientists are subject to the will of scientific directors or university rectors? A new appeal was thus filed, this time with the State Council (Consiglio di Stato), which again struck it down. This time the motivations for the ruling appeared more strictly procedural, though admittedly bizarre. The three scientists were in fact deemed once again not to have standing for the appeal, but in this case because they had not submitted a proposal to the call against which they were appealing. But how and why could they have applied for a call that explicitly excluded their projects?

The case is not yet settled, but its proceedings already reveal the contours of a fundamental dispute over the scope of research freedom and the relative power ascribed to individual scientists or governmental agencies in shaping its course. In order to bring these contours into sharper relief, I will now apply a comparative approach and examine a strikingly parallel dispute in the US.

[19] E. Cattaneo - E. Cerbai - S. Garagna, *L'assurda censura anti-staminali*, in «La Stampa», 16 December 2009, p. 23.

2. *The US: reframing the essence of scientific research*

The case is *Sherley v. Sebelius* and it recently ignited heated controversy with a decision by the US district court for the District of Columbia[20]. The background is the political battle on hESC research, one of the most divisive issues in American politics since 1998, when James Thompson first isolated hESC, and their potential for regenerative medicine was recognised by the international scientific community. In the summer of 2001 President Bush announced his policy on hESC that limited federal funding only to those hESC lines that had been derived prior to the cut off date of August 9. In the spring of 2009 President Obama issued an executive order to reverse Bush's policy and permit the National Institutes of Health (NIH), the US federal agency that both supports and conducts medical research, to pursue hESC research. To that end, the NIH was asked to draft new guidelines on the conduct and funding of hESC research. These came into effect in July 2009 and allowed «funding for research using human embryonic stem cells that were derived from human embryos created by *in vitro* fertilization (IVF) for reproductive purposes and that were no longer needed for that purpose»[21].

Two stem cell scientists known for their opposition to hESC research, James Sherley and Theresa Deisher, filed a suit to obtain a preliminary injunction that would prevent the NIH guidelines from taking effect and thus unleash a substantial increase in federal support for hESC research. The injunction was granted on 23 August 2010 by Chief Judge Lamberth of U.S. District Court for the District of Columbia. The key argument brought by the scientists was that the NIH guidelines violated the Dickey-Wicker Amendment, a part of an Act passed by Congress in 1996 that prohibited the use of federal funds for «(1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on foetuses in utero» under existing federal regulations. Since 1996, Congress has never modified this Amendment and has always renewed it in the yearly funding bill for Health and Human Services,

[20] Sherley v. Sebelius, 704 F. Supp. 2d 63 (D.D.C. 2010).

[21] *National Institutes of Health Guidelines for Human Embryonic Stem Cell Research*, 74 Fed. Reg. 18,578, April 23, 2009.

thus making it a cornerstone of US policy on embryo research. Since 1999, the NIH had been interpreting the prohibitions entailed in the Amendment as not applicable to hESC research *per se* but only to the process of deriving hESC from embryos. A clear demarcation line was thereby drawn between the destruction of embryos that yields hESC (and whose funding is forbidden under Dickey-Wicker) and the research on hESC that was framed by NIH as not entailing any embryo destruction. In their legal challenge, Sherley and Deisher instead maintained that hESC research did result in embryo destruction and thereby violated the Dickey-Wicker Amendment.

The strategy of the NIH defence was to argue that the definition of 'research' formulated in the Dickey-Wicker Amendment was ambiguous and that – therefore the NIH, as a governmental agency, was entitled to freedom of interpretation under the doctrine of Chevron deferense. Under Chevron, the principle laid out in *Chevron U.S.A. Inc., v. Natural Resources Defense Counsel, Inc.,* courts must first assess whether Congress has «directly spoken to the precise question at issue»[22]. Only if «the statute is silent or ambiguous» must the court defer to NIH's interpretation, as long as it remains «based on a permissible construction of the statute».

Judge Lamberth was however unpersuaded by this line of argument and instead found the Dickey-Wickey Amendment to be unambiguous, arguing that the term «research ... has only one meaning, i.e., a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalisable knowledge»[23]. Having established that, in Dickey-Wickey, Congress had «directly spoken to the precise question at issue» without ambiguities, the court proceeded to examine the remaining question, namely whether ESC research was «research in which a human embryo is destroyed», thereby violating the Dickey-Wicker Amendment. The NIH presented its interpretation of the term 'research' in Dickey-Wickey as meaning «a piece of research». ESC derivation from embryos and their subsequent use would be distinct pieces of research, and hence NIH funding of the latter piece would not breach Dickey-Wicker's prohibition of the

[22] Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837 (1984).

[23] Sherley v. Sebelius, 704 F. Supp. 2d 63 (D.D.C. 2010).

former piece. On this point the court delivered the most substantial aspect of the judgment, engaging in an ontological deliberation of what scientific research is. The notion that research could be broken down into separate pieces was discarded, and research was interpreted as an indivisible, whole process of investigation.

Seventeen days after the injunction had been granted, the appeal court placed it temporarily on hold, restoring NIH funding for hESC research, which however remained in a limbo until 29 April 2011, when the appeal court overturned the injunction of 2010. And on 27 July 2011, the same Chief Judge Lamberth of the US District Court for the District of Columbia issued the decision that acknowledged the higher court's opinion and overruled the previous injunction[24].

Beyond the final legal settlement, however, what is important for our analysis is to ask what was the motivation behind Sherley and Deisher's suit and, more importantly, why was the court prepared to grant them a preliminary injunction that would alter hESC federal funding so dramatically. Sherley and Deisher work exclusively with adult stem cells and are vocal opponents of hESC research. They claimed that the new NIH guidelines, by allowing federal funding for hESC, would increase the competition among scientists for NIH research grants and would thus jeopardize their chances of obtaining funds for their laboratories. Strikingly, the court was prepared to recognise this claim as a truly imminent injury, a danger so clear and present as to require immediate action to prevent «irreparable harm».

From this comparison it is apparent that the Italian and the US cases present striking symmetries, though they actually seem like reverse symmetries in which the actors and their claims run counter to each other.

The initial symmetry is that in both cases scientists take legal action to overturn the decision of a governmental agency regulating hESC research, challenging the scope of research endorsed by the respective governments. In Italy, Cattaneo, Cerbai and Garagna opposed the Health Ministry's decision to exclude hESC research from funding despite its being legal in Italy. In the US, Sherley and Deisher opposed the NIH decision to include hESC in its funding policy. And here we note the first marked difference in this symmetry: whereas the Italian scientists

[24] M. WADMAN, *Court Quashes Stem-cell Lawsuit*, in «Nature», 476, 2011, p. 14.

fought to expand the repertoire of research tools available to the stem cell community, the Americans strove to restrict it – a difference that becomes salient when one considers the specific situation of the scientists involved. In the Italian case Cattaneo, Cerbai and Garagna were excluded from funding and sought, through their suit, to make it available in principle to all colleagues. In the US Sherley and Deisher were funded under the current scheme and sought to prevent the application of the new guidelines in order to prevent other colleagues from accessing funding and thereby increasing competition.

Finally, in both the Italian and the US case, the courts reinscribed the ontology of research. In Italy, we witness the reframing of research as an activity carried out by individual scientists who lose, however, any individual right to pursue it in freedom. The scope of their freedom becomes predicated upon the hierarchical structure of research institutions that alone can challenge governmental decisions. In the US, scientists instead retained the ability to challenge governmental decisions as individual citizens. Yet adjudication of the case proceeded through a radical reframing of the very essence of research whereby the definition of its fundamental phases (in this case the derivation and later use of hESC) transcended the boundaries of scientific expertise and governmental discretion and ended up being settled in court.

V. Conclusions

We have examined three critical developments in the Italian polity's confrontation with hESC. From the empirical analysis we may now describe how the Italian civic epistemology has evolved around this controversial biotechnological topic, which has occupied Western democracies for the last fifteen years. Specifically, and consistently with our initial aims, this analysis enables us to distinguish salient articulations in the role played by stem cell scientists and, more broadly, in the relationship of scientific expertise to public accountability and political decision-making.

The proceedings of the Dulbecco Commission on stem cells embody the classic paradigm of technocratic expertise and its relationship with political power. Scientists were recruited as experts in an advisory role that was by and large insulated from a direct confrontation with the

various stake-holders. Their work was by no means a simple regulatory exercise, and, as we have seen, the Commission's most innovative contribution was its reinterpretation of the ontology and epistemology of somatic cell nuclear transfer (SCNT). When the Commission unanimously endorsed SCNT as an ethically unproblematic source of embryonic stem cells, it did so by deliberating on the ontology itself of the product of SCNT, reframing it as an extension of the patient's body rather than an embryo. And it reached this conclusion through an epistemic weighing of its properties whereby the artificiality of SCNT became the key feature that removed its product from the trajectory of nascent human life and reassigned it to the safer harbour of somatic repair. But this epistemological moment was civic and public only insofar as the scientists, philosophers and theologians engaged in this epistemic exercise had been appointed by the Minister of Health and could therefore be considered to be related, albeit very indirectly, to the democratic vote that led to the Minister's appointment. It was civic epistemology, but citizens saw through the eyes of few selected experts.

The referendum campaign instead represents a fuller, and perhaps inevitably messier, manifestation of civic epistemology. Here the question of the scientific merit of hESC, and implicitly also the ontological and normative questions about the status of the human embryo, were posed directly to Italian citizens. The familiar complaint that the public does not understand such technically loaded issues does all but reinforce the significance of such moments in the structuring of any biopolity. After all, as Lippman argued,

«... it is controversies of this kind, the hardest controversies to disentangle, that the public is called in to judge. Where the facts are most obscure, where precedents are lacking, where novelty and confusion pervade everything, the public in all its unfitness is compelled to make its most important decisions. The hardest problems are those which institutions cannot handle. They are the public's problems»[25].

But how did the Italian public come to know whether it wanted to endorse hESC and what their merits were in the first place? As I have shown, scientific expertise as well as the vigorous mobilisation of the Catholic Church both played a crucial role in articulating the public debate. On each side of the divide, the opposing camps resorted to scientific evidence in order to legitimise their value claims. Indeed, we

[25] W. LIPPMAN, *The Phantom Public*, New Brunswick NJ 1993 (1925[1]), p. 121.

can see how one of the most effective rhetorical slogans commissioned by the Catholic Church («Life cannot be put to the vote») also captured the broader discourse that pervaded the referendum campaign, namely the purported dissociation of values from facts, of normative stances from scientific observations. Scientific expertise was then recruited as a key resource to license knowledge claims and inspire ethical conducts in televised debates. If the referendum could be fought over facts, scientists became natural candidates to see those facts and interpret them on behalf of the public. While similar trends have been followed in many countries, what appears more distinctive of the Italian situation is the unforeseen and highly effective alliance of the Catholic Church with scientific expertise. Needless to say, this alliance also heralded the overt emergence of advocate scientists, experts who openly engage in the political battle, bringing their own expertise to bear on the framing of the issues under debate. Whilst in the case of the Dulbecco Commission expertise descended on the polity from the high citadel of governmental advice, during the referendum campaign expertise flowed through the media system and aligned itself along the cleavages of the debate. When life begins, whether adult stem cells can transdifferentiate, whether adult and embryonic stem cells have the same medical potential: these became the 'factual' themes on which the various political actors recruited and mobilized scientific expertise. The media in turn played a critical role in casting these 'factual' controversies into their well-oiled televised templates, able to stage, for each topic, a balanced fight among rivals on equal footing. Indeed, it was the cleansing power of 'facts' that elevated the opinions of the few scientists opposing hESC research – a vocal minority at both the national and international level – to the same level as those of the overwhelming majority of scientists endorsing hESC as a viable research option. The stage was set for the public representation of a bitterly divided scientific community, whose evidence claims could serve the normative agendas of one or the other camp. In one of the most value-laden referendums in Italian history, scientific expertise became the key resource to articulate conflict while at the same time deflating its political and moral implications.

Finally, in the legal suit over stem cell funding, we have seen a third instantiation of the political role of scientists and a final confrontation over the shape of the Italian civic epistemology. And the comparison with the symmetrical case in the US has helped us sharpen the salient

features of the problem and articulate the far-reaching implications of the legal reasoning that underlie both legal cases. In both of them, the controversy concerned issues quintessential for knowledge-based societies: who is entitled to decide what to know, and what are the limits of this power. It is practically undisputed that the executive power decides how to allocate research funding according to broad priorities perceived to serve the national interest. But once this first choice about the knowable has been taken, how much epistemology should a government legitimately pursue? How much say should it have on the most appropriate tools to pursue the various research priorities? And where does the epistemic threshold lie between executive authority and scientific expertise?

Seen from this angle, the two legal cases are interesting because they both feature a form of scientist advocacy even deeper than the one sketched above. It is of course true that both groups of scientists were fighting for their respective front (respectively pro-hESC or against-hESC in Italy and the US), though we should bear in mind the fundamental asymmetry between the two situations (Italian scientists wanted to expand the scope of stem cell research, while their American colleagues acted to restrict the breadth of the field). But beyond this obvious level of advocacy, similar to the one witnessed during the referendum campaign, here the deeper level of scientists' engagement is the direct contestation of executive choices. In other words, in both cases, and while claiming a specific right to research, scientists also fought on a broader front, challenging the judiciary to define the limits and scope of executive interventions in scientists' activity. As a consequence, what emerges from these cases is also an ontological appraisal of what constitutes research and what the limits of its freedom are. In the US, the court's decision to restrict federal funding for hESC research counteracted the NIH's interpretation of the Dickey-Wicker Amendment and framed hESC research as a single knowledge endeavour in which the act of deriving hESC could not be disjoined from their subsequent analysis. One may cheer or bemoan the specific outcome, but at a broader level, what emerges is the possibility, for an individual scientist, to challenge the government's epistemology, both in its scientific interpretations and in its funding priorities. Also in Italy it is ultimately the judiciary that fulfils the task of defining the scope of research freedom, though the obvious differences between the American and the Italian legal systems make the

ontological deliberation over what constitutes research less explicit in the Italian case. Nonetheless, the defeat of the Cattaneo suit (pending the final decision) marks a critical moment in the articulation of the Italian civic epistemology, since scientific freedom emerges as severely constrained. It is no longer the individual scientist, contrary to the US scenario, who can challenge the executive epistemology and reclaim his/her freedom of research. Rather, the fundamental right to research freedom is shifted from the individual level of the citizen scientist to the institutional level of academic institutions, thereby diluting its distinctive strength and its specific potential. And the executive power emerges strengthened in its centralized control of not only research priorities but also epistemic choices.

Stem Cells: The Italian Way to Bioethics

by *Luca Marini* *

At the beginning of the 1990s, bioethics in Italy was a mysterious subject restricted to a handful of specialists who could afford the luxury of studying the ethical, social and legal issues arising from the progress of biomedicine and biotechnologies without concerning themselves about the repercussions of their research results in the media and politics. Cloning still belonged to the realm of science fiction; the debate on medically assisted reproduction (or, if the Catholic formula is preferred, on artificial insemination) was still far from finding legislative solution; informed consent – which at that time was discussed with exclusive reference to clinical trials – had not yet shown signs of the hypertrophy which would fifteen years later characterize the debate on «advance health-care declarations» (or if the secular formula is preferred, «living wills»). In general, bioethical issues received little coverage in the press; and they were generally ignored by the media (and politicians).

The start-up phase of Italian bioethics lasted until the second half of the1990s, when research on embryo stem cells conducted by virtue of its (concrete or hoped-for) applied and therapeutic uses directed the attention of specialists to what would subsequently be regarded as the paramount bioethical issue: the embryo, as well as definition of its status and its protection. Thereafter, and until 2007 (when discussion on the «beginning of life» abruptly gave way to that on the «end of life», for reasons discussed later), the bioethical debate was concentrated on the implications of embryo stem cell research[1].

* «Ad Personam» Jean Monnet Chair of Biolaw at the University of Rome «La Sapienza», Vice-President of the Italian National Bioethics Committee, President of European Centre for Science, Ethics and Law (ECSEL).

[1] For an overview on the last twenty years of bioethical, biolegal and biopolitical debate in Italy see L. MARINI, *Codice del diritto internazionale e comunitario della bioetica*, Torino 2009, from the introduction to which I have drawn the following discussion in the main text. For a survey of the sources of international and EC law on bioethics see L. MARINI, *Il diritto internazionale e comunitario della bioetica*, Torino 2006.

In the meantime, outside Italy matters were changing in the (bio)legal and normative sphere. Devised at international and European Community level, well before that of domestic law, were legally binding instruments concerning bioethics: from the *Convention on Human Rights and Biomedicine*, negotiated within the Council of Europe from 1990 onwards, signed at Oviedo in April 1997 and which came into effect in December 1999[2], to the EC Directive on the legal protection of biotechnological inventions, approved in 1998 after a ten-year progress through the Parliament and the Council of Ministers of the European Community. If one considers that the *Oviedo Convention*, as a framework-convention, has a very wide range of application and deals with matters (for instance, advance health-care directives) that in Italy would acquire salience only several years later; if one considers that the EC Directive on biotechnological patents took, as said, ten years to reach enactment (the first proposal by the European Commission dates to the end of the 1980s); and if one considers that the biotechnological patent is a 'horizontal' issue in that it underlies or links with numerous other bioethical problems ... then one understands not only the foresight, but also the logical-systematic consistency and the strategic pragmatism with which the international institutions (and, with them, scholars of international law) have presided over the birth and development of «bioethical law». This was to the detriment of Italian institutions and scholars of domestic law, although it was not until the 2005 referen-

[2] The *Oviedo Convention* (entitled *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*; or *Convention pour la protection des droits de l'homme et de la dignité de l'être humain à l'égard des applications de la biologie et de la médecine: Convention sur les droits de l'homme et la biomédecine*) is also widely referred to as *Convenzione di bioetica* (*Convention on Bioethics*) in Italy. This expression is not only inaccurate, it is also dangerously ambiguous because it has heightened the lexical and conceptual confusion consequent on the contributions of various disciplines (medical, philosophical and juridical in particular) to the bioethical debate. This confusion, which is evident in the first Italian handbooks on clinical and philosophical bioethics (where the sources, subjects and procedures in regard to EC law community are indicated with great imprecision) has given rise not only to sterile competition between legal norms and deontological rules, but also to the tendency to conceive and apply bioethical norms for the purpose more of corporative protection than social mediation. The obvious reference is to the attention paid to the 'proceduralization' of informed consent and its consequences for protection of the doctor's professional liability. Also obvious is the reference to the «prescriptive bioethics» treated below.

dum concerning the law on medically assisted reproduction that they discovered bioethics and, simultaneously, its (bio)political implications.

This difference in the speeds – international and domestic – of the bioethical and biolegal debate gave rise in Italy to a generation of researchers little concerned with the evolution of the international debate, and it led to the development of markedly dogmatic approaches to bioethical issues, which were framed for the general public mainly in terms of their cultural, ideological and confessional significance, as well as their political spendability. There thus arose what I call «the Italian way» to bioethics and biolaw, which has developed, primarily if not exclusively, on two dimensions: 'life's beginning' (cloning, stem cell research, embryo), where the Catholic principle of defence of human life from its conception onwards is opposed by the secular principle of freedom of research; and 'life's end' (refusal of treatment, living will, euthanasia), where the secular principle of the patient's self-determination is opposed by the Catholic principle of the inalienability of the body and life.

The «Italian way» as just defined, besides fostering attitudes and positions sometimes paradoxical also at the biopolitical level, has exacerbated the semantic, legal and political exploitation of uncertain and controversial scientific issues, thereby severely prejudicing the widely-urged redefinition of the relationship between science and civil society[3]. To illustrate this point, I shall examine the case of cloning and research on embryo stem cells, which concerns the period from the end of the 1990s to the present day (although, as said, since 2007 the issue of stem cell research has given way to other bioethical and biopolitical 'emergencies').

It is necessary first to recall the extremes of the debate which has accompanied the birth and development of embryo stem cell research: on the one hand, the Catholics, opposed to any form of experimentation on embryo stem cells, considered to be the expression of human life and therefore endowed with a dignity and rights like those of human

[3] That the dogmatic dimension of bioethical issues tends to prevail over all others is confirmed by the events, between 2007 and 2009 which led to the replacement of the vice-chairpersons (among them the present writer) of the Italian National Bioethics Committee (Comitato Nazionale per la Bioetica-CNB). The paradoxical outcome was an increase in the number of CNB vice-chairpersons, which was contrary to the «more functional arrangement» that was the purported reason for the replacement.

beings; on the other, the secular advocates of freedom of scientific research also on embryo stem cells, considered simply as biological material useful for the development of clinical and therapeutic applications. Given the anthropological and cultural importance of the issue, the debate on embryo stem cells has had the merit – perhaps for the first time to such a large extent – of prompting collective reflection on themes of fundamental importance for contemporary society, such as the governance of research and scientific communication. Less meritorious is the fact that this debate, because of its indubitable biopolitical importance, has conferred on bioethical reflection and its institutional arenas a role epistemologically extraneous to them. They are no longer descriptive of the scientific evidence and of the ethical options necessary to direct normative policy choices concerning the sustainability of certain techno-industrial developments in scientific progress; instead they are directly authorizative (some would say «prescriptive») of directions and tendencies in scientific research itself.

This is a striking anomaly, not so much because bioethical reflection must restrict itself to furnishing advisory opinions without ever translating them into binding decisions, even on the biolegal level[4], as because limits or prohibitions should concern not research in itself (unless the intention is to limit or condition scientific progress) but the technological, industrial and commercial applications of the results of that research. Nevertheless, also in order not to act contrary to the interests of the techno-industrial lobbies, the opposing dogmatisms recurrent in biopolitics have claimed to draw from the bioethical debate conducted in the institutional bodies (and sometimes with their acquiescence) restrictions and prohibitions applicable to those areas of scientific research allegedly of greatest concern to the general public. Accordingly, it may have been purely for biopolitical reasons and purposes, and certainly not biolegal ones, that the prohibition of the cloning technique, ratified by the first additional protocol to the *Oviedo Convention*, has been

[4] For that matter, a development of this kind would be nothing new in the Italian legal system: suffice it to recall the profound change of competences and functions imposed on hospital bioethics committees by the 1998 legislation on the clinical trialling of drugs, which provoked controversy also within the CNB (for details see L. MARINI, *I Comitati etici per la sperimentazione clinica di medicinali. Competenze nella normativa comunitaria e nazionale*, Roma 2001). Moreover, for years pending in Parliament are bills for the creation of independent regulatory authorities on bioethics and biotechnologies like those of other countries.

publicized as an obstacle against research on embryo stem cells: that is, on the research most likely (or at least claimed to be such) to find therapies for otherwise incurable diseases[5].

This misunderstanding of the role of bioethics, which largely reflects the hendiadys of science and technology consolidated in recent years, has contributed not only to the distortion of the bioethical debate but also to exploitation of the competences and functions (and deliberative procedures) of bodies like the Comitato Nazionale per la Bioetica (CNB, which advises the Italian government), accelerating their transformation in preparation for their probable – and widely hoped-for – abolition[6].

It should also be pointed out that the issues of embryo stem cell research and cloning intertwine not only at the logical and techno-scientific level but also at the biopolitical and biolegal one. Some years ago, I called attention to the reason as to why Italy has not deposited with the competent international authorities the instrument ratifying and implementing the *Oviedo Convention* (constituted by law 145 of 28 March 2001)[7]. The reason is that the aforementioned deposit would not only have entailed transposition into Italian law of the Convention, which forbids the creation of embryos for research purposes[8], but also of its first additional protocol, which bans human cloning

[5] Significantly, this is echoed in the EC Directive on the legal protection of biotechnological inventions (considered ultra-liberal by Catholic bioethics), article 6, paragraph 1 of which prohibits the patenting of biotechnological inventions if their commercial exploitation would be contrary to the public order or morality, as would be, for example, the patenting of human cloning procedures. Aside from the meanings of expressions such as «public order» and «morality», it is evident that the prohibition applies not to biotechnological inventions resulting from scientific research but to techno-industrial and commercial applications contrary to the general public interest.

[6] Suffice it to point out that candidatures for the «authorities» mentioned at note 4 have already been lodged.

[7] Law no. 145/2001, published in «Gazzetta Ufficiale», no. 95 of 24 April 2001, ratifies the *Oviedo Convention*, as well as the *Additional Protocol* on prohibition of the cloning of human beings. The law has not yet been deposited in compliance with article 33, paragraph 2, of the *Oviedo Convention*.

[8] See article 18, paragraph 2, of the *Oviedo Convention*, according to which «The creation of human embryos for research purposes is prohibited» («la constitution d'embryons humains aux fins de recerche est interdite»). Paragraph 1 of the same article states that where the law allows research on embryos *in vitro*, it shall ensure adequate protection («protection adéquate») of the embryo.

outright[9]. To be noted is that this is a prohibition which applies to human cloning as a technique in itself, with no distinctions in regard to its purposes: that is, without distinction between therapeutic cloning and reproductive cloning – expressions which became current in scientific media communication at the end of the 1990s[10]. This delay and hesitation, besides relieving Italy from observance of the dispositions of the *Oviedo Convention*, produced what I have elsewhere described as the first (and most significant) paradox of Italian biopolitics. In fact, whilst it is easy to understand why political forces in favour of cloning should oppose the filing of Italy's ratification and execution of the *Oviedo Convention* and its additional protocol (the necessary condition for transposition of the convention, with its prohibition of cloning, into Italian law), it is less easy to understand why so much favour was shown towards the cloning technique – subject to patents and strongly supported by the techno-industrial lobbies – by those political forces (called «progressive» at the beginning of the bioethical debate) that had been traditionally critical of industry and business. Equally paradoxical was the stance taken by those political forces (called «conservative» at the beginning of the bioethical debate), which, although traditionally close to the interests of the free market, opposed cloning and embryo

[9] See article 1 of the *Additional Protocol* «on the prohibition of cloning human beings» («portant interdiction du clonage d'êtres humains»), according to which «Any intervention seeking to create a human being genetically identical to another human being, whether living or dead, is prohibited» («est interdite toute intervention ayant pour but de créer un être humain génétiquement identique à un autre être humain vivant ou mort»).

[10] The reasons for this distinction, captious from the legal point of view, can be summarized as follows. Who does not remember the announcement, subsequently proved bogus, of the birth of the first cloned human being (the child «Eva») made by the Raelians, a religious movement according to which extraterrestrials had created life on Earth by means of genetic engineering techniques which would in turn make immortality possible? It could be maliciously argued that the media visibility of this case was carefully planned, perhaps also to induce public opinion to condemn «reproductive» cloning (which would favour the aspirations to immortality of only the few) and instead to support «therapeutic» cloning (which would foster the development of new therapies to the benefit of the many). Whatever the case may be, since the end of the 1990s numerous scholars (even jurists) and large part of public opinion have erroneously believed that the prohibition of cloning enshrined in the *Additional Protocol* to the *Oviedo Convention* applies only to reproductive cloning. On the other hand, numerous scholars (even jurists) believe, once again erroneously, that the *Oviedo Convention* has entered into force in Italy.

stem cell research in defence of the embryo and consequently pressed for deposit of the instrument ratifying the *Oviedo Convention*[11].

Definition of the embryo's status – the paramount bioethical and biolegal problem – was made even more complex by the inadequacy of certain international and European Community legal instruments which, until the end of the 1990s, made indiscriminate use, even within same provisions, of expressions such as «human being», «human person» and «individual»[12]. The traditional equivalence of such expressions in law was rapidly called into question by techno-scientific progress, given the identification, from the 1980s onwards, of increasingly precocious stages of embryonic development (the so-called «pre-embryonic stages») and the consequent creation of scientific neologisms with meanings widely exploited by the media (but often incomprehensible to the general public, as in the case of «ootid»)[13]; and by the more recent possibility of creating «chimera embryos», that is, human-animal genetic hybrids[14].

[11] To be added is that the above-mentioned «conservative» forces have in recent years reconsidered their traditional adherence to not only the ideal but also the objectives and instruments of European integration. They have done so on the one hand because of the financial support that the Community institutions furnish to scientific research on embryo stem cells, and on the other, because of the EC directives intended to create, also through the establishment of private banks of human cells and tissues (so-called «biobanks»), a common market for such biological materials. The reference is obviously to Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. On this see L. MARINI, *Biobanche di cellule staminali tra norme comunitarie e disciplina nazionale*, in *Diritto del commercio internazionale*, 2007, pp. 893 ff.

[12] See, for example, article 1 of the *Oviedo Convention*: «Parties to this Convention shall protect the dignity ... of all *human beings* and guarantee *everyone* ... respect for their integrity» («Les Parties à la presente Convention protègent l'*être humain* dans sa dignité ... et garantissent a toute *personne* ... le respect de son intégrité ...» (emphasis added).

[13] The CNB has devoted an *ad hoc* document to the ootid which, regardless of the scientific base of the neologism, and the *quorum* expressed by the CNB in approval of the document, has had the effect (in the media and biopolitics) of legitimating the use of the neologism and further popularizing it.

[14] Whilst, for biolegal purposes, some consider the embryo to be an «individual» (by virtue of its biological individuality, although this is not entirely accepted scientifically), according to others the embryo cannot, for the same purposes, be considered a «human person» (on account of its incapacity for interpersonal relations). To be added is that

Significantly, the response by international and EC law to the question of the uncertain and increasingly controversial scientific definition of the embryo has produced further and perhaps even greater inadequacies in biolaw. Since the early 2000s – that is, as the concrete applications of embryo stem cell research have become increasingly apparent – international (and particularly EC) laws have altered, sometimes abruptly, their lexicon, using the expression «human person» to define the range of application of their biolegal provisions and expressly forbidding only «reproductive cloning»[15]. Apart from the major consequence of excluding the embryo from such legal protection, this development signifies the extension to the field of biolaw of an eminently dogmatic approach – one, moreover, not always functional to the ends pursued. It is evident, in fact, that if biolegal norms are to be effective beyond their ideological and political impact, they should codify controversial and constantly changing scientific notions. Instead, they have often done no more than recognize purely conventional, and therefore arbitrary, facts and values[16]. Moreover, bearing in mind the chronic delay with

also the apparently generally endorsed definition of the embryo as a «human being» is showing its limitations in regard to the above-mentioned possibility to create hybrids and chimeras.

[15] It is useful to recapitulate the stages in the gradual and progressive impoverishment of the guarantees granted to the embryo, particularly within the framework of EC legal instruments: in 1998, the *Directive on the Legal Protection of Biotechnological Inventions* (much criticised in regard to its envisaged patentability of the human body, also in embryonic form: see article 5, paragraphs 1 and 2) prohibited the patenting of human cloning procedures; in 2000, the *Nice Charter* (hailed as a new European decalogue of fundamental rights) prohibited only «reproductive cloning»; in 2004, the so-called *European Constitutional Treaty* (whose Preamble, and therefore the non-binding part, should have contained a reference to the «Christian roots» of Europe) reformulated the Nice Charter and expressly granted to the «person» the guarantees that the Charter granted to the «individual»; in 2007, with a view to approval of the Treaty of Lisbon, the Nice Charter was «adapted» to resume the formulation introduced by the *European Constitutional Treaty*, which has not come into effect. For details see my *Il diritto internazionale e comunitario della bioetica*, pp. 58 ff., as well as pp. 69 ff.

[16] The first example of «biolegal dogmatism» is provided – well before the issues of cloning and embryo stem cells arose – by the EC regulations on the marketing of foodstuffs constituted by or derived from GMOs. These regulations, in fact, require the labels of food products to state the presence of genetically modified material when it exceeds a given threshold of tolerance (0.9%). It is obvious that this threshold, in the absence of reliable scientific data on the presumed or real harmfulness of GMOs, is purely conventional and, therefore, arbitrary. On this see L. MARINI, *OGM, precau-*

which the law follows techno-scientific progress, such norms have proved largely to be compromises and do not contribute to resolving (to the advantage of some or other party) the hermeneutic and applicative problems so evident in the matter considered: given the uncertain and controversial scientific definition of embryo stem cells (are they human or biological?), do the ootid and the chimera constitute real scientific progress or rather a technologically advanced attempt to elude possible prohibitions on creating embryos for the purposes of research? Again, would a law that forbids today, as in Italy[17], the creation of hybrids and chimeras be applicable tomorrow to the new hybrids that techno-scientific progress already prefigures?[18].

Finally, it is undeniable that the issues of cloning and embryo stem cell research has, as said, shifted the focus of bioethical debate from the scientific and moral dimension to that of communication and popularization. This has bred the tendency, subsequently applied to an increasing number of bioethical issues, to exploit in semantic and media terms controversial and controvertible scientific evidence which is badly understood and communicated, thereby hampering the formation of informed and responsible public opinion on matters ultimately dominated by industrial and commercial interests able to shape (when not to create *ex novo*) cultural and political-normative choices and attitudes[19].

zione e coesistenza: verso un approccio (bio)politicamente corretto?, in «Rivista giuridica dell'ambiente», 2007, pp. 1 ff.

[17] In Italy, article 13, paragraph 3, letter d), of law no. 40/2004 prohibits «the fertilisation of a human gamete with a gamete of a different species and the production of hybrids or chimeras», but without defining the scientific notions of hybrid or chimera.

[18] Consider the convergence among biotechnologies, nanotechnologies and cognitive science and the possible consequences of such convergence (empowerment of the human body, robotics, the so-called «post-human»), which from the realm of pure science fiction is becoming a technological, industrial and commercial reality.

[19] This the case of the alleged right to a child, which is clearly inspired by the progress of artificial insemination techniques, and by the assisted reproduction business. Similar considerations apply to the business of predictive tests and the planning of a baby's genetic characteristics for therapeutic purposes. On this see L. MARINI, *Diritto al figlio e tutela giuridica della vita prenatale* (Right to a child and legal protection of human life), in «Etica per le professioni», 1, 2005, pp. 31-41 (Published, for reasons unknown to me, with the title *Salvaguardare il valore della vita umana* [Protecting the value of human life] and accompanied by editorial boxes incoherent with the sense of the article. Perhaps, this is another move of the Italian way of bioethics!).

In particular, those who have exploited the public debate on cloning and embryo stem cell research have not only impeded information and awareness about these issues[20], they have also fuelled a media uproar which has obstructed scientists in their search for scientifically and ethically neutral solutions, where possible. This is the case of cellular reprogramming, which would reverse the biological clock of stem cells and bring the adult ones back to the embryonic stage (resolving the bioethical problems thus far described). Researchers have achieved this result only since the dogmatic debate on the embryo has substantially attenuated (opening the way to the debate on the living will). They have done so for the following reasons.

The debate on the embryo (which in Italy has helped increase academic and political visibility) began to subside, until it disappeared from media coverage in 2007, the year which saw the apparent defeat of Catholic bioethics in regard to embryo stem cell research. 2007, in fact, began with approval of the Seventh Framework Programme for Research and Technological Development, which, unlike the previous Sixth Framework Programme, expressly regulated the funding of research that uses stem cells derived from embryos produced for the purpose of medically assisted reproduction and left unused (so-called «surplus embryos»)[21].

[20] Suffice it to recall the bewilderment of Italian public opinion on the occasion of the referendum to abrogate law no. 40/2004: one might ask how much was understood then, and how much is remembered today, about the referendary questions.

[21] In 2002, the *Sixth Framework Programme* introduced a moratorium on the funding of research using embryo stem cells, accompanied by a significant exception – although this expired at the beginning of 2004. The exception, which raised the issue of biobanks storing human cells and tissues, concerned «banked or isolated human stem cells in culture» existing on 30 September 2002 (see the minutes of the Council meeting of 20 September 2002, Annex F to the European Commission document SEC (2003) 441 of 3 April 2003, p. 90). It is significant that, as regards the bioethical dimension of the aforementioned exception, the then Minister of Research requested the CNB to expressly pronounce on the matter. Not so his successor, however, who withdrew the Italian Government's support for the «minority block» within the Community Council of Ministers, which, if it had continued, would have prevented approval of the Seventh Framework Programme and the funding of research using surplus embryos (for details see L. MARINI, *Il diritto internazionale e comunitario della bioetica*, pp. 203 ff.). Finally to be pointed out is the specifically biopolitical significance of the fact that, to render homage in some way to the prohibition enacted by article 18, paragraph 2, of the *Oviedo Convention*, the *Seventh Framework Programme* excluded from EC financial support research using embryos expressly created for the purpose of scientific

Apparently beaten, the Catholic forces reacted in more organized and effective manner than in the past, being helped to do so by a change of government in 2008. They devised a strategy that although not original, was soon able to monopolize the debate and to force the lay parties to engage in a wearying media pursuit. The strategy was based on comparisons among controversial (and little understood by the non-expert) scientific findings – as had previously happened in the debate on GMOs – and on the endeavour to minimize the scientific evidence contrary to that sustained in the biopolitical contingency[22].

This strategy, which was also widely used in debate on the harvesting and storage of umbilical cord blood stem cells – another area of bio-political controversy in 2007 and 2008[23] – nevertheless had the result

research: the European Community, in fact, is not a party to the Oviedo Convention and is therefore not bound to observance of its provisions.

[22] In other words, whilst for secular scientists embryo stem cells are more promising in terms of (presumed or real) therapeutic applications, for Catholic scientists the more sustainable research (from the ethical and scientific point of view, but also in financial terms) is that on adult stem cells (somatic cells derived from amniotic fluid and the umbilical cord blood); that is, cells obtained from ethically neutral sources. On contradictions in this approach, with particular regard to umbilical cord blood stem cells, see the following note.

[23] Initially considered one of the few bipartisan bioethical issues, the storage of umbilical cord blood cells soon became associated with new forms of the human body's commodification. This came about because the EC Directive laying down quality and safety standards for the harvesting, storage, and use of human cells and tissues (issued in 2002, adopted in 2004, and transposed into Italian law in 2007) envisages forms of indemnity for donors. Thus, faced with the prospect of donations of cells and tissues for payment, and with the prospect of storage for a fee (with a view to unspecified uses) of such biological material in private biobanks (often devoid of specific medical and biomedical competences), Catholic forces stigmatized the scientific uncertainty surrounding therapeutic applications of umbilical cord blood cells stored for autologous purposes (i.e. to the benefit of the same person from whom the cells are harvested). They acknowledged that scientific evidence supported the storage of such biological materials, but maintained that such storage should be for solidarist purposes and in public biobanks. In Italy, the controversial scientific dimension of this issue interweaves with regulations widely regarded as inadequate, not only in formal terms (given that they merely consist in a ministerial ordinance constantly reiterated since 2002), but also in substantive ones, since it is thought that ordinance prohibits Italian citizens from doing in Italy what it allows them to do in foreign countries (autologous storage in private biobanks). Beyond the bandying about of scientific data which fuels futile oppositions between public and private and, once again, alternates utopias with promises of extraordinary therapeutic applications – and also beyond the real clinical utility of

(perhaps not entirely unpredictable) of confusing public opinion, which progressively lost interest not only in the debate on identifying the stem cell source best suited to scientific and therapeutic purposes (embryonic stem cells? adult stem cells? umbilical cord blood stem cells?) but also in the dogmatic positions taken up in that debate. This was one of the reasons why, just as the embryo showed signs of losing its importance in the bioethical and biolegal domain, there arose, on the one hand, electoral and political programmes based on its protection (which also resumed, without success, the vexed question of abortion) and, on the other, the proposal to the public of new dogmatic issues with which to catalyse biopolitical discussion, in keeping with the «Italian way» defined earlier. It was in this context that there developed, and rapidly attracted media attention, the debate on «advanced health-care declarations» (or, according to lay persons, «living wills» or «advanced health-care directives»); a debate which once again enhanced political and parliamentary visibility[24].

Finally to emphasised the bipolarism between life's beginning and life's end in bioethics came about despite the efforts of those – unfortunately few – who tried, in line with the international debate of the time, to direct attention to other issues no less important from the point of view of the health and psycho-physical wellbeing of human beings. Suffice it to mention the technological, industrial and commercial implications, also for medicine, of nanotechnologies and telemedicine (which were also the subject of documents issued by the CNB), to understand what issues have not only been obscured by the «dogmatic reductionism»

cord blood cells (in the meantime, according to the scientific «evidence», superseded by other cell sources) – the issue in question has marked an important transition. It has done so firstly because this bioethical issue has affected hundreds of thousands of citizens in Europe; and secondly because it has induced some bioethicists (especially those enamoured of the European ideal) to reconsider the ends and means of European Community integration, it being by now evident that the principle of the freedom of circulation, which for thirty years has underpinned the European common market, applies to human cells and tissues as well.

[24] Significant in this regard is the title of a conference promoted by the Commissione Igiene e Sanità of the Italian Senate and held in Rome on 29 March 2007: «Testamento biologico: le dichiarazioni anticipate di volontà sui trattamenti sanitari» («The living will: advanced declarations on the medical treatment desired»), where the punctuation is strategically used, from a communicative and biopolitical perspective, to support a non-existent conceptual equivalence.

which I have mentioned, but also underestimated – sometimes deliberately – by a certain section of the press, to the detriment of the culture of objective and scientifically-grounded information and, ultimately, to the formation of truly well-informed and aware public opinion[25].

This last aspect brings us the crux of the bioethical debate, because bioethical themes are by now subject to communicative strategies functional to political objectives. This once again raises the problem of how to promote a culture of objective, impartial, and scientifically-grounded communication. In a country of 'castes' like Italy, is certain that the issue of the communication will not be resolved within the current generation. But in this regard, I cannot but recall one of the most neglected dispositions of the *Orviedo Convention*, which instead underpins the entire pactional normative corpus, with its effects on national legal systems. I refer to article 28 of the Convention, which obliges states party to the convention to ensure that questions raised by bio-medical progress are the subject of appropriate public discussion and consultation[26]. Perhaps, in Italy, the objective of creating an informed and aware public opinion has not been achieved precisely because the *Oviedo Convention* has not yet been transposed into national law ... but I wouldn't bet on it!

Together with the problem of promoting objective and sound scientific communication, there are other problems that are still unresolved:

[25] It is odd that the documents on nanotechnologies and on telemedicine were among the few (if not the only) texts approved by the CNB between 2002 and 2006 which were not the subject of specially arranged press conferences (for the CNB documents see the website www.governo.it/bioetica). The example of nanotechnologies, in particular, is emblematic of the dogmatic reductionism described in the main text. I brought the topic to the CNB's attention in 2002, but the work of the *ad hoc* group had to wait until approval of law no. 40/2004 on medically assisted procreation. The relative advisory opinion was approved only in June 2006, during the last plenary assembly of the CNB then in office.

[26] See article 28 of the *Oviedo Convention*, according to which «Parties ... shall see to it that the fundamental questions raised by the developments of biology and medicine are the subject of appropriate public discussion in the light ... of relevant medical, social, economic, ethical and legal implications, and that their possible application is made the subject of appropriate consultation» («les Parties ... veillent à ce que les questions fondamentales posées par les développements de la biologie et de la médecine fassent l'objet d'un débat public approprié à la lumière .. des implications medicale, sociales, économiques, éthiques et juridiques pertinentes, et que leurs possible applications fassent l'objet de consultations appropriées»).

– the academic codification of bioethics and biolaw, which if they remain feebly and anachronistically confined to current scientific-disciplinary sectors (philosophy of law, legal medicine and history of medicine for the former; civil law for the latter), the opportunity will have been missed to open up to new knowledge produced in emerging sectors (nanotechnologies, robotics, neurosciences);

– the risk of a «bioethical business», of which worrying signs are already apparent. Recent years, in fact, have seen increasing demand for specific consultancy services matched by a supply backed by disciplines not traditionally engaged in the exercise of professional activities, as well as being, by their nature, extraneous to the analysis and the scientific and interdisciplinary evaluation of problems concerning collective and inter-generational ethics (for example, environment, food and health safety);

– the construction of new hierarchies among needs of general interest increasingly set on a collision course. I refer to the protection of health and the environment, on the one hand, and to the freedom of economic initiative and industrial development on the other[27];

– the increasingly concrete risk of the subordination of legal instruments to economic globalization processes which tend, by their nature, to have the interests of the market predominate over human well-being and rights[28];

[27] See on this the Action Plan on nanotechnologies adopted by the European Commission in June 2005 and entitled *Nanosciences and Nanotechnologies: An Action Plan for Europe 2005-2009*, whose purpose was to support industrial and commercial development in the sector. Although the regulation of nanotechnologies cannot elude application of the precautionary principle, in consideration of the uncertainty of the scientific data relative to the potential risks of nanotechnological applications, the Action Plan cited the above-mentioned principle but distorted its sense by restricting its application to «*realistic* risks of a certain gravity» (emphasis added). Suffice it to point out that, in fact, the Communication of the European Commission on the precautionary principle, adopted in 2000, stated that the principle applies in all cases in which preliminary objective scientific evaluation indicates that there are reasonable grounds for concern that «the *potentially* dangerous effects» (emphasis added) may harm the health of the environment, human beings, animals and plants, but the scientific data do not allow detailed evaluation of the risk.

[28] This risk is made explicit by comparison between article 2 of the 1997 *Oviedo Convention* and article 3, letter b), of the 2005 UNESCO *Universal Declaration on bioethics*. According to the Convention «The interests and welfare of the human be-

– the wavering stance of biopolitics due to its constant use of the criterion of broad and 'politically correct' consensus in the political and institutional management of bioethical issues. Obviously, this criterion, usable instrumentally in dealing with the media, is entirely unsuited to the scientific evaluation of such issues;

– finally, the constant exploitation of bioethical persons and facts, according to a tradition that, not only in this field, afflicts Italy, where it is difficult to tolerate cultural autonomy or of any other kind because it is not functional to defence of (or support for) constantly changing ideological or corporative positions. That bioethics is by now also a classification parameter or a political or ideological indicator is, I believe, an objectively well-founded belief because it is confirmed by emblematic and unequivocal episodes in which I was involved, in my capacity as deputy president of the CNB, between 2007 and 2009.

Solution of the above problems requires scientific efforts, a willingness to debate, cultural and judgemental autonomy, awareness of the collective interest, combined with determination and energy and clearly-stated policies which I fail to discern in a country like Italy where self-referentiality, by the individual or group, is an aspiration and a goal.

ing *shall* prevail over the sole interest of society or science» («L'intérêt e le bien de l'être humain *doivent* prévaloir sur le seul intérêt de la société ou de la science»), while the Declaration states that «The interests and welfare of the individual *should* have priority over the sole interest of science or society» («Les intérêts et le bien-être de l'individu *devraient* l'emporter sur le seul intérêt de la science ou de la société» [emphasis added]). Note also the use, respectively, of the expressions «human being» and «individual» («être humain» and «individu»), in line with what was stated above in the main text and at note 14. Also the international codes of ethics manifest a similar tendency. The first edition of the Geneva Declaration, adopted in 1948 by the World Medical Association as a revised version of the Hippocratic Oath, committed the doctor to preserving the «health and *life*» of the patient, as well as to maintaining the utmost respect for human life «from the time of its *conception*» (emphasis added). Subsequent amendments of the Declaration expunged the reference to the patient's «life» and replaced «conception» (which clearly raises the problem of protecting the embryo) with the term «beginning.»

Index of Names

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