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Differing Routes to Stem Cell Research: Germany and Italy

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Contents

INTRODUCTION

- The Weight of the Past, by *Renato G. Mazzolini* p. 9
A Revolution in Biology?, by *Hans-Jörg Rheinberger* 13

HISTORICAL PERSPECTIVES

- Where Does Stem Cell Research Stem from? A Terminological
Analysis of the First Ninety Years, by *Ariane Dröschner* 19
Stem Cells, Reversibility and Reprogramming: Historical
Perspectives, by *Christina Brandt* 55

THE GERMAN CASE

- The Public Debate on Stem Cells Research in Germany. «Und
bloß kein Dambruch» / «For Heaven's Sake Avoid a Breach
of the Dam», by *Alexandra Schwarzkopf* 95
Legal Developments in Stem Cell Research in Germany, by
Jochen Taupitz 131
Appendix: The German Law 156
Stem Cell Research in Germany with Specific Regard to Human
Embryonic Stem Cells, by *Anna M. Wobus* and *Peter Löser* 165

THE ITALIAN CASE

- Embedding Society in Cells: Science, Ethics and Politics in
the Italian Public Debate on Stem Cell Research, by *Lorenzo
Beltrame* 191

Stem Cells and the Structuring of the Italian Biopolity, by <i>Giuseppe Testa</i>	p. 225
Stem Cells: The Italian Way to Bioethics, by <i>Luca Marini</i>	251
Index of Names	267

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 lines¹. 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 phenomena². 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 understanding³. 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.