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Cloning and Stem Cell Debates in the Context of Genetic Determinism

Jane Maienschein *

When I studied introductory biology at the newly-coeducated Yale in the early 1970s, we didn't hear anything about stem cells. For that matter, we heard relatively little about embryos and development and much more about genetics and cell biology. The impression given was that cells are complex, they divide and multiply, and together they make up organisms. What seemed to matter most, however, were the genes, the nucleus, and to some extent the ways that genes cause the cells to act. Led by cell biologist J.P. Trinkaus, our course placed more emphasis on the interactions of cells than most courses of the time, but cell-cell interaction was not the central theme.

In biology generally, and certainly in the public mind, the "central dogma" of genetics had already taken hold and has only gained strength since. The message was that understanding biology must start with DNA, RNA, and their actions in producing proteins. Genes direct cells to develop, differentiate, and divide. Understanding development must start with the first cell, the egg cell, as it undergoes meiosis and casts off half its chromosomes in preparation for the fertilization process. Each cell division brings expression of different genes, and expression of these genes causes all the organic processes. And so it goes. Genes are inherited and they drive development; what follows is caused by heredity, or the doctrine of genetic determinism.

Or so it has seemed since DNA and genetics assumed a core place in biology in the 1960s and 1970s. What had been called embryology, or the study of embryos, became known instead as developmental biology and developmental genetics. The older emphasis on morphogenesis, differentiation, and cellular changes took a back seat to presumptions of genetic determinism as the cause of those developmental processes. My contention is that this emphasis on genetic determinism has reinforced a popular misconception that what matters about the life of an individual organism, including its form and function, is laid out fully in all relevant respects with fertilization, at the time that the full complement of chromosomes comes together from the two parents. This mistake is serious, since development actually occurs gradually, depends from the beginning on the

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environmental context and on cell-cell interaction to guide and inform the process, and is an epigenetic process that unfolds over time as the complex system develops.

To help address problematic genetic determinist views and to understand why they are problematic, this Article provides an historical look at the evolution of ideas of development. Rather than progressing through a recitation of chronology, however, the approach focuses on several clusters of contributions. Part I examines cloning and demonstrates what was meant by cloning, why the research developed, and with what results. Then came excitement about cloning combined with hopes for stem cell research for producing therapies—all in the context of genetic determinism. In Part II, I turn to issues of underlying assumptions and how they affect our understanding of life. In particular, genetic determinism and the assumption that development and differentiation occur in only one irreversible direction have caused problems. Part III looks in more detail at stem cell research as an alternative to genetic determinism and brings us to the nature of developmental science and who should count as an expert in this field. Finally, I present my conclusions.

I. EARLY CLONING RESEARCH

My first embryology course in graduate school was at Indiana University with Robert Briggs. Working with Thomas King in the early 1950s, Briggs had carried out the first successful cloning by nuclear transfer, which he performed using frogs.¹ King and Briggs transferred the nucleus from very early embryo stages of one species into the egg of another species and observed that the resulting frog was more like the donor than the host.

Researchers, especially John Gurdon, carried this nuclear transplantation technique further, even using cells from later stage embryos. Gurdon's frogs appeared on magazine covers, a large dark colored female and the small albino males, suggesting that the nucleus of the donor prevails at least in these visible respects over the influence of the host egg.² Gurdon had success with nuclei from somewhat later stages, reporting that about 30% of the nuclei transferred from blastula stages produced tadpoles, while 6% of nuclei taken from hatched tadpoles and only 3% from the even later stage of swimming tadpoles could produce successful clones that themselves developed to the tadpole stage.³ This may seem like a small percentage, but note that Briggs and King had not had success with any later stage nuclei and had concluded that cloning is difficult and

1. Robert Briggs & Thomas J. King, *Transplantation of Living Nuclei from Blastula Cells into Enucleated Frogs' Eggs*, 38 PROC. NAT'L ACAD. SCI. 455 (1952).

2. See, e.g., Anne McLaren, *Cloning: Pathways to a Pluripotent Future*, 288 SCIENCE 1775 (2000).

3. *Id.* at 1776.

that cloning from the late stages was not possible.⁴ By the 1960s, "cloning" in this sense, by nuclear transfer, was a well-established research technique, allowing transfer of a nucleus from one individual to another in order to test the relative contributions of donor and host, and in order to assess the ability of the experimental system to respond to changing conditions.

As I began to do research with Briggs, he talked about this research into cloning. Why, he asked, was there so little public interest in the possibilities for cloning, perhaps even for reproductive reasons? He pointed to old magazines that showed a brief public attention to the experimentally produced hybrid frogs, but noted that publicity had declined quickly. Briggs felt that any cloning for reproductive reasons would surely raise ethical questions about what sorts of things scientists ought to do. He did not dismiss the possibility that nuclear transfer might be possible with human eggs, since he did not make the assumption as many researchers did that mammals (including humans) were too complex for nuclear transfer to be successful. Nor did he assume that any frog resulting from nuclear transfer would be like the donor nucleus rather than like the host embryo, since he was not a nuclear (or genetic) determinist. Instead he taught that developing embryos were highly responsive to their environments and that we knew little about the details of development. He was an embryologist who understood the complexities of the embryo and its ability to respond and adapt to changing environmental conditions. Briggs understood that, in science generally, we should expect the unexpected and keep exploring the range of what is possible; we must retain open minds about what science can achieve.

Briggs also noted that he and King had not been the first to imagine animal cloning through nuclear transfer. Embryologist Hans Spemann had raised the idea in 1938 in his Silliman Lectures presented at Yale. He had suggested a "fantastical" experiment⁵ that he did not think should be terribly technically difficult. Spemann was thinking of frogs, which have large eggs that are plentiful and easy to work with. Already Spemann could transplant parts of different embryos and watch the resulting hybrid grow. Therefore, why not carry the transplantation one step further and transplant not just limbs and eye sockets but also a nucleus? He imagined that it would be possible to take a nucleus from one egg or embryo and transfer it to another that had had its embryo removed. Spemann never carried out his proposed experiment, but Briggs, King, and Gurdon did.

James Watson and colleagues may have had a typical geneticist's skepticism about the significance of animal cloning in their 1983 textbook, *Recombinant DNA: A Short Course*. Describing nuclear transfer in animals such as frogs in early developmental stages, they wrote, "In the immediate future there is little

4. *Id.* See generally J.B. Gurdon & Alan Colman, *The Future of Cloning*, 402 NATURE 743 (1999) (reflecting on early cloning research).

5. HANS SPEMANN, EMBRYONIC DEVELOPMENT AND INDUCTION 211 (1938).

likelihood of nuclear transplantation being attempted with any other mammalian species." They also noted, "If the efficiency and reproducibility can be improved, the method may, however, find a place in animal breeding. In theory it could be attempted with human eggs and embryonic cells, but for what reason? There is no practical application."⁶

No practical application for cloning? At the time, that conclusion could well have seemed sensible to geneticists not particularly interested in development or in frogs. Yet embryologists surely thought otherwise, since there was much interest in tools that could help us understand the developmental stages and the processes of morphogenesis and differentiation that take place gradually over time. Cloning in the sense of embryonic nuclear transfer, in fact, has proven itself useful as one such tool, and 1997 brought cloning to the public's attention.

In that year, Ian Wilmut and his team announced that they had cloned Dolly the sheep using nuclear transfer. This was the same basic technique that Briggs and King had pioneered, except that Wilmut and his team used adult somatic cells for the donor nuclei instead of nuclei from early developmental stages. Wilmut did not start with Briggs's and King's assumption that later stage nuclei would be too far differentiated and therefore a mismatch for the egg.⁷ In fact, the many biologists who had made that standard assumption were shocked that Wilmut's laboratory's technique worked. Princeton Professor of Microbiology Lee Silver commented to *New York Times* reporter Gina Kolata that he had just completed a book claiming that such somatic cell nuclear transfer was impossible. As Gina Kolata reported, "It's unbelievable," Dr. Silver said. "It basically means that there are no limits. It means all of science fiction is true. They said it could never be done and now here it is, done before the year 2000."⁸ Obviously, he was forced to revise the book that he had just been ready to send to press.⁹

Wilmut's group showed that cloning was indeed possible with adult mammals. Additionally, they showed that cloning had a practical application, namely in agriculture. Why not try to duplicate a cow that produces especially large quantities of milk? Why not replicate the cattle with the best beef, the fastest thoroughbreds, or the best-laying chickens? Agriculture had many uses for

6. JAMES D. WATSON, JOHN TOOZE & DAVID T. JURTZ, *RECOMBINANT DNA: A SHORT COURSE* 207-08 (1983).

7. For discussion of these discoveries, see IAN WILMUT, KEITH CAMPBELL & COLIN TUDGE, *THE SECOND CREATION: DOLLY AND THE AGE OF BIOLOGICAL CONTROL* (2000). Ian Wilmut later explained that his colleague Keith Campbell was the leader on the project and that others in the team also contributed in important ways.

8. Gina Kolata, *Scientist Reports First Cloning Ever of Adult Mammal*, N.Y. TIMES, Feb. 23, 1997, at A1.

9. See LEE M. SILVER, *REMAKING EDEN: CLONING AND BEYOND IN A BRAVE NEW WORLD* (1997); Kolata, *supra* note 8.

somatic cell nuclear transfer. Some also saw the potential for the cloning of endangered species, at least for those where natural habitat still existed to allow benefit from a breeding program.

Of course, cloning adult humans is another matter. There was a strong public reaction against the idea of genetic copying or the prospects for what Gina Kolata imagined and many others echoed as a "time-delayed twin."¹⁰ Few were troubled by the ethics of cloning sheep or cows, and some found the idea of cloning a favorite pet appealing. It was the prospect of human or other mammalian reproductive cloning that led to widespread debate all across the globe. Despite some initial curiosity and some rogue interests in individuals imagining cloning themselves, a strong consensus emerged by the end of 1997 among scientists that there was little reason for cloning humans for reproductive reasons.¹¹ Too many risks, too many unknowns, and too few justifications were already leading to a dominant view that this was one area of science that we should not carry out. We should not want to, nor need to clone human beings.

This conclusion, reinforced by all the well-funded bioethics discussions of the previous decade about the Human Genome Project, was that cloning involved genetic duplication, that genetics defined an individual's life, and that therefore a genetic duplication of persons would be morally and pragmatically unacceptable. Some felt that legislation prohibiting human reproductive cloning was warranted or perhaps that the 1974 National Research Act governing human subjects research already prohibited such experimentation.¹² Some hoped that the moral force of public opinion against cloning would prevail. With no compelling interests in human cloning, it seemed in 1997 that it was just a matter of working out details for prohibiting human cloning, ideally internationally.

This turned out to be not so easy, in large part because of the successes of stem cell research. We need to look at that work that began in 1998, when we learned about human embryonic stem cell research for the first time through the

10. Kolata, *supra* note 8.

11. See, e.g., NAT'L BIOETHICS ADVISORY COMM'N, CLONING HUMAN BEINGS (1997), available at <http://bioethics.georgetown.edu/nbac/pubs/cloning1/cloning.pdf> ("It seems clear to all of us . . . that any attempt to clone human beings . . . is unacceptably dangerous to the fetus and, therefore, morally unacceptable."); Andy Coghlan, *Cloning Report Leaves Loophole*, NEW SCIENTIST, June 14, 1997, at 77 (summarizing the conclusions of the National Bioethics Advisory Commission and noting the panel agreed that human cloning presented "unacceptable risks"); CNN Interactive, Scientist: Human Cloning 'Need Not Happen,' <http://www.cnn.com/TECH/9703/12/cloning.news/index.html> (last visited Apr. 21, 2009) (quoting Ian Wilmut saying in 1997 that human cloning "need not happen, and I hope it will not").

12. National Research Act, Pub. L. No. 93-348, § 201, 88 Stat. 348 (1974) (codified as amended in scattered sections of 42 U.S.C.) (establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which later promulgated regulations for human subjects research (codified at 45 C.F.R. § 46 (2009))).

work of James Thomson and John Gearhart. Research had been underway for decades on mice, but the public had generally remained ignorant about stem cells. Thomson and Gearhart showed that the research on mice could now be extended to humans, and thus, they raised the possibility that stem cell lines might prove of therapeutic use,¹³ even if not for purposes of reproducing "copies" of the cloned donor animal.

Thomson's work on human embryonic stem cells and Gearhart's work on human embryonic germ cells was announced against the background of heated discussions about cloning. Immediately and repeatedly, television and print news coverage combined the two. What did stem cell research mean for cloning, and what did research cloning mean for stem cell applications? After all, both are about embryos. The two lines of research were, naturally enough, conflated in the public mind. Those who had decided for whatever reasons that they hated the very idea of cloning immediately also hated stem cell research. Those intrigued by the scientific possibilities for cloning saw even greater prospects in combining the two. The neologism "therapeutic cloning" was created to describe cloning-for-research-purposes-only in order to separate it from "reproductive cloning," which would aim to produce babies. With so-called therapeutic cloning came the hope that the public imagination could be captured by the "therapeutic" opportunities rather than by the lingering negative of imagined duplicated humans.¹⁴ Developmental biologists never lost sight of the research value in cloning, but they did lose control over the use of the technical term. The geneticist Lee Silver, for example, reported that a television producer had told him in 1998: "Dr. Silver, you are not aware of what cloning can accomplish. Clones are not what you think they are."¹⁵

Stem cell research may have great potential application. Yet it has also led people to fall back on assumptions of genetic determinism and cloning. Geneticists have thought in terms of hereditary determinism, whereas stem cell researchers and developmental biologists have worked from assumptions of developmental plasticity, or the idea that it is the process of development in the context of changing environments that shapes the resulting organism along with the original inherited information. This idea of developmental plasticity is critical for stem cell research, which involves being able to direct undifferentiated stem cells to become different kinds of cells, depending on the environment of their

13. See, e.g., John Gearhart, *New Potential for Human Embryonic Stem Cells*, 282 SCIENCE 1061 (1998); Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT'L ACAD. SCI. 13,726 (1998); James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE 1145 (1998).

14. See, e.g., David Magnus & Mildred K. Cho, *Issues in Oocyte Donation for Stem Cell Research*, 308 SCIENCE 1747, 1747-48 (2005).

15. Lee M. Silver, *What Are Clones? They're Not What You Think They Are*, 412 NATURE 21, 21 (2001).

culture medium. Yet assumptions of genetic determinism had come so overwhelmingly to dominate biology, and public impressions of life, that even fundamental work in areas of what had earlier been called embryology, such as the work by Briggs, King, and Spemann, was largely ignored.

In fact, those working in the embryological tradition had always realized that embryos retained a great deal of developmental plasticity and that they can respond and "regulate" within their changing environmental conditions. These researchers had continued to ask fundamental questions about differentiation and morphogenesis. They also recognized the special properties of stem cells to produce "immortal" undifferentiated cell lines while also being able to become differentiated under the right conditions. This is the idea of pluripotent stem cells: that under some conditions in the laboratory dish they can self-replicate forever (or so it is assumed), and with different culture media they can be made to become specific different kinds of differentiated cells (and have plural potential).

While some of these embryological scientists continued with their developmental studies, by the 1970s many researchers had followed the lure of genetics and molecular biology and set aside the complex system of cellular interactions that make up embryology. The Human Genome Project had so tipped the public perception, and some might argue even the actual practice, of biology that geneticists seemed to be able to serve as the experts for all matters of living organisms. Reporters turned to the familiar geneticists like Nobel Prize winner James Watson or familiar bioethicists, who had been enticed by the NIH's Ethical, Legal, and Social Implications (ELSI) genomics program to focus on genetics, as the appropriate "talking head" experts to help interpret stem cell science.¹⁶ In fact, however, many of those researchers knew far less about the details of early development than developmental biologists would have, and their lack of expertise sometimes led to misinformation and confusion. Naturally enough, when scientists seemed to be contradicting each other or even correcting themselves, the appearance of professional confusion led to public annoyance and distrust. Why should the public, members of Congress, or reporters trust scientists who could not agree? It has taken some time for developmental biologists to emerge as legitimate authorities and experts in developmental biology and to help interpret the complexities of the developing organic systems.

To understand this particular situation more clearly, and also to look forward wisely, it will help to understand a bit more history. In particular, we need to appreciate the impact of underlying assumptions both in the scientific research and among the public, and why these assumptions matter. It matters greatly that genetic determinism came to dominate biology as well as the public

16. For example, Gina Kolata, in first breaking the cloning story for the *New York Times*, turned to geneticist and molecular biologist Lee Silver rather than a developmental biologist to explain the events. See Kolata, *supra* note 8.

perception of life. And it matters greatly that with genetic determinism has come an assumption that development is a matter of progressive differentiation caused by genes and expressed in the proper genetically-regulated sequence.

II. FUNDAMENTAL ASSUMPTIONS: GENETIC DETERMINISM AND UNIDIRECTIONAL DIFFERENTIATION

Where direct knowledge is impossible, biologists necessarily start working from assumptions. It is important to articulate and understand the impact of those assumptions, insofar as that is possible. Sometimes the assumptions become so widespread and well-established that it is difficult to get outside what Thomas Kuhn called the basic working assumptions of a paradigm.¹⁷ Yet it is valuable to try. This section examines genetic determinism and unidirectional differentiation, two such assumptions in stem cell research. This section also discusses the difference between genetic determinism, the approach that primarily emphasizes the role of genes in development, and epigenesis which emphasizes the ways that cells may develop in response to contextual factors independent of inherited genes.

Since the early twentieth century, it has become commonplace to assume that each individual organism begins with inherited genes, located in the nucleus and organized along chromosomes. The genes, it seems, carry the information, or code, for the resulting characteristics of the organism. Development follows, with the cells in each developmental stage expressing (or becoming differentiated according to the instructions of) the appropriate piece of information programmed in the genetic code. The dominant assumptions of twentieth-century biology, therefore, included genetic determinism and the idea that differentiation occurs in one direction only, following the genetic program.

In the early twentieth century, hereditarians who held that characters are determined by their heredity (through genetics) led to an enthusiasm for eugenics as an effective approach to solving the perceived public health problem of a contaminated gene pool. Fortunately it became clear that we really knew little about inheritance, and the ill-advised eugenics programs mostly declined.¹⁸ By mid-century, however, James Watson and Francis Crick's discovery of DNA structure quickly made it clear that "it has not escaped our notice that the specific pairing" of the nucleotides that make up DNA "immediately suggests a possible copying mechanism for the genetic material."¹⁹ Heredity drives development, it seemed, and "defective" genes could be a new target for elimination, which many

17. THOMAS S. KUHN, *THE STRUCTURE OF SCIENTIFIC REVOLUTIONS* 23 (1962).

18. For an excellent overview, see DIANE B. PAUL, *CONTROLLING HUMAN HEREDITY: 1865 TO THE PRESENT* (1995).

19. J.D. Watson & F.H.C. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 *NATURE* 737, 737 (1953).

critics considered a new form of eugenics.²⁰

With these assumptions in place, genetics became the backbone for teaching biology. The traditional problems of embryology, differentiation, and morphogenesis largely gave way to primacy for problems of molecules, genes, and cell biology. Of course, some researchers continued their studies of developmental patterns, including studies of stem cells: it has remained a core goal of biology to understand how, once we have particular genes, they are actually expressed. Most public attention remains focused on news about genetic correlations with diseases or hopes for genetically-based personalized medicine.

Molecular and cell biology programs are widely recognized as having proliferated in academic institutions, but they often require little understanding of the processes by which cells differentiate over time or of relationships among cells, organisms, and species. The implication of this investment is that if only we knew the human genome sequence, then we could solve medical problems. The Human Genome Project was certainly justified, given the availability of techniques for studying genetics and then genomics. But the single-minded focus on genetic determinism has had consequences.

The second fundamental assumption—the inevitability of unidirectional differentiation—is reinforced by the assumption of genetic determinism. When we watch a fertilized egg develop through each successive stage, it is natural to see it as becoming more differentiated. It is not unreasonable to see the process of increasing differentiation as determined by some internal driver (the genes are today's choice, even though earlier generations tried invoking internal gradients and other chemical factors). And it is also reasonable to see the process as unidirectional. Once cells and body parts are appropriately differentiated, the natural assumption is that they stay differentiated. That is what we seem to see under normal conditions, and it is reasonable to assume that that is the way differentiation works. Why would differentiation be other than in the progressive and forward direction of increasing cell specialization and organismal complexity?

Yet in the absence of all the data we have today, the late nineteenth and early twentieth century biologists experienced great disagreement about this point. Some researchers such as August Weismann and Wilhelm Roux were strong hereditary determinists, but theirs was the minority position.²¹ Weismann and Roux believed that the individual inherited its germ plasm from both parents, and the hypothetical units (called determinants by Weismann) that made up the nuclear chromosomes were then divided into the different cells during cell division. They hypothesized that the determinants were actually parceled out,

20. See, e.g., *THE CODE OF CODES: SCIENTIFIC AND SOCIAL ISSUES IN THE HUMAN GENOME PROJECT* (Daniel J. Kevles & Leroy Hood eds., 1992); ROBERT COOK-DEEGAN, *THE GENE WARS: SCIENCE, POLITICS AND THE HUMAN GENOME* (1994).

21. JANE MAIENSCHIN, *WHOSE VIEW OF LIFE* 72-74 (2003).

yielding a mosaic of different cells. Even when it became clear that the complete chromosomal complement remained whole in each cell, however, they just invoked a selective expression of different determinants in each cell. Their overarching view was, in effect, consistent with genetic theory today.

But others—indeed the vast majority of embryologists and histologists (as cell biologists were called then)—complained that Weismann and Roux provided no explanation of development at all.²² These researchers saw complexities, responses to changing environmental conditions, and interactions among cells and parts. Development was not predetermined by inheritance, they concluded, but was a gradual response of the integrated and interactive whole organism to its changing environment. As Edmund Beecher Wilson acknowledged in the title of his classic, *The Cell in Development and Inheritance*, an organism needs both that which is inherited—the germ cells with their nuclear chromosomes—and the capacity to respond to the particular conditions.²³ For these biologists, development was an epigenetic process and not a matter of preformationism or even the sort of internal predeterminism that Weismann and Roux offered. They explicitly and repeatedly rejected such a hereditarian account as hypothetical, not grounded in evidence, and as too simplistic to explain the complexities of development and differentiation.²⁴

This has been a core debate about the nature of life reaching back to Aristotle. William Morton Wheeler summarized debates about Weismann's ideas in 1899 by suggesting that there are two different kinds of thinkers. Some see change and process, while others see stability. Heraclitus, Aristotle, physiology, and epigenesis characterize one way of looking at the world; Parmenides, Plato, morphology, and preformationism characterize the other. These are, Wheeler felt, stable and persistent classes, and yet the nature and details of their differences have changed over time. Wheeler argued that by the end of the nineteenth century neither a strict preformationist nor a strict epigeneticist who ignored new evidence and new reasoning could succeed. In the end, it is not to philosophy but to science that we must look to resolve the relative contributions of hereditary pre-determinism and regulatory development, for "[b]oth tendencies will find their correctives in investigation."²⁵

Today, we are in a similar situation except that the preformism of genetic determinism has overbalanced our understanding of complex developmental

22. For a summary, see EDMUND BEECHER WILSON, *THE CELL IN DEVELOPMENT AND INHERITANCE* 303-31 (1st ed. 1896).

23. EDMUND BEECHER WILSON, *THE CELL IN DEVELOPMENT AND INHERITANCE* (2d ed. 1900). This volume was later retitled. *THE CELL IN HEREDITY AND DEVELOPMENT* (3d ed. 1925).

24. For discussion, see JANE MAIENSCHIN, *TRANSFORMING TRADITIONS IN AMERICAN BIOLOGY, 1890-1915* (1991).

25. William Morton Wheeler, *Caspar Friedrich Wolff and the Theoria Generationis*, in *DEFINING BIOLOGY: LECTURES FROM THE 1890S*, at 195, 216 (Jane Maienschein ed., 1986).

processes. We have forgotten Wheeler's plea for a balanced view. We have forgotten that when Hans Driesch shook apart the first two cells of the sea urchin egg, they did not result in two half embryos, as Roux had predicted, but instead in two smaller larval urchins.²⁶ We have forgotten the extensive work that Thomas Hunt Morgan did on regeneration of a large number of different animals, showing the extent of developmental plasticity.²⁷ We have even forgotten the work of John Tyler Bonner on morphogenesis and the relations of parts in the developing interacting organism.²⁸ These studies show the capacity of the individual to regulate its development in the context of environmental change, even with experimental assaults like shaking apart the first two cells or chopping up the embryo into bits of organism like earthworms to watch them regenerate into two new worms.

Biologists have also forgotten the early work on stem cells and their developmental plasticity. It is worth reminding ourselves of this work, if only to help illuminate the power of the underlying assumptions. If biologists had had these earlier studies more clearly in mind, or if reporters had called on experts who knew this developmental research rather than appealing mainly to geneticists, the public might not have been so shocked by the cloning and stem cell discoveries of the late 1990s. They might even have been able to forestall the preformationist conclusions that fit so tidily with ultra-conservative religious assumption that life begins absolutely at the moment of fertilization or "conception"—the moment of genetic union—even though the now-fertilized egg remains completely undifferentiated and unformed.²⁹

This is the key point: the biology that we have actively and visibly promoted (and with which the public is most familiar) is a biology that relies heavily on predeterminism. Until the public appearance of human stem cell lines, we did not see the biology of epigenetic development or the sort of moderated balance that Wheeler called for over a century ago. If some scientists claim that each organism begins with inheritance of genes, with development simply expressing the genetically preprogrammed sequence of steps, it is difficult to explain the complexities of developmental processes to those in the public who insist as a matter of faith that "life begins at conception." It is ironic that those who most vehemently insist that they are "pro-life" in all its forms are those adopting a biological determinism and denying the "free will" of developmental plasticity of

26. Hans Driesch, *Entwicklungsmechanische Studien. I. Der Werth der beiden ersten Furchungszellen in der Echinodermmentwicklung. Experimentelle Erzeugen von Theil- und Doppelbildung*, 53 ZEITSCHRIFT FÜR WISSENSCHAFTLICHE ZOOLOGIE 160-78 (1892), translated in FOUNDATIONS OF EXPERIMENTAL EMBRYOLOGY 38-50 (Benjamin Willier & Jane M. Oppenheimer eds., 1964).

27. See THOMAS HUNT MORGAN, REGENERATION (1901).

28. See JOHN TYLER BONNER, MORPHOGENESIS (1952).

29. MAIENSCHIN, *supra* note 21, at 3.

the individual. This view of genetically determined life is probably not, in fact, what they have in mind. We must make this point clear in order to gain wise traction on the problem of competing entrenched views. To understand the alternatives, let us look briefly at the history of stem cell science.

III. STEM CELL HISTORY: AN EPIGENETIC ALTERNATIVE

Like cloning, stem cell research did not suddenly begin out of nothing in 1998. In fact, also like the term "cloning," the term "stem cell" was first used in the late nineteenth century. Both concepts began in botany where cloning meant production of identical individual plants. Stem cells referred to undifferentiated cells that retained their undifferentiated state. Edmund Beecher Wilson and his friend and collaborator William Sedgwick were the first ones to use the term in the late 1800s.³⁰ They did not, of course, know about the range of different types of stem cells that we have identified since, nor did they culture stem cell lines or look at mammalian cells. Yet they identified the original concept, and other research in embryology and cytology later confirmed that some cells retain flexibility and the ability to respond to environmental conditions.

Ross Granville Harrison, working first at Johns Hopkins and then at Yale, carried out the first successful tissue culture experiment, which was also the first stem cell experiment.³¹ He did not label the neuroblasts (embryonic cells that give rise to neural cells) that he cultured "stem cells," nor did he develop a stem cell line or any of the other key elements we use today to define the cells. In retrospect, however, this was the first stem cell experiment, using cells that we recognize as neural stem cells and carrying out the first ever cell and tissue culture.

Harrison asked a core embryological question: how does a cell differentiate? In particular, he wanted to shed light on the heated contemporary debate about the nervous system. The question was, how do individual cells "know" where to go? Do they follow predetermined paths that are laid down in the developing embryo? Or, in contrast to this preformationist view, could the process be epigenetic? That is, might the cells develop independently, each following its own internal direction to a point but taking its cues from the surrounding environment? In this case, was it the interactions of the whole organism that influence how each cell develops? Preformation or epigenesis: this was the old question in a new form.

30. See, e.g., 16 OXFORD ENGLISH DICTIONARY 627 (2d ed. 1989) (defining "stem" and noting early references to the term "stem cell," including an 1896 reference from E.B. Wilson that distinguishes stem cells from somatic cells) (quoting WILSON, *supra* note 22, at 111). For further discussion, see Jane Maienschein, *What's in a Name: Embryos, Clones, and Stem Cells*, 2 AM. J. BIOETHICS 12 (2002).

31. MAIENSCHIEIN, *supra* note 24, at 261-89.

Harrison followed the same reasoning as Spemann, looking to discover the results of transplanting cells. Instead of transplanting such parts as limbs from one embryo to another, which is what researchers had done in the past, and instead of transplanting the nucleus as Spemann had suggested, Harrison proposed to go further. Why not actually explant the cells? Just take them out of the body altogether. Might it not be possible to take those cells known to give rise to the nerve fibers (the neuroblasts), remove them from their normal surroundings, place them into a culture medium, and see what they will do? If they behave more or less normally, this would suggest that they follow an epigenetic interaction with their environment as they grow under normal conditions, as in the experimental case. Harrison concluded that the nature of the processes was fundamentally the same and that more research was needed to discover the other factors involved. This experiment was not easy, and Harrison first had to develop a culture medium on which the cells could grow. Fortunately, he moved to Yale in 1907 and was temporarily housed near the bacteriologists. They taught him about aseptic conditions, and his technique improved dramatically.³²

Harrison decided that he had obtained what he wanted from the experiment, namely another piece of evidence about the epigenetic nature of development. He did not pursue tissue culture further because he was interested in different questions that called for different methods. Yet others did take up the approach, notably Alexis Carrel at the Rockefeller University.³³ He and other tissue culture researchers set down the foundations for later stem cell research, establishing techniques for successful cell culture and demonstrating the considerable plasticity and ability to respond to surrounding conditions of many types of cells and tissues.

That was a foundation, but it was the work on hematopoietic stem cells that started serious interest in human stem cells and their potential applications. Already in the eighteenth century, some adventurous experimenters had apparently carried out animal to human blood transfusions, though the earliest rumors are not well documented. In 1795, Philip Syng Physick reported having transfused blood from one human to another for the first time. This broke down any assumption that humans were entirely unique and instead showed a common physiology. In the twentieth century, blood transfusions became routine as researchers worked out ways to control immune responses, to recognize and match blood types, and to prevent clotting.³⁴ Yet despite this great advance,

32. See Ross Granville Harrison, *The Outgrowth of the Nerve Fiber as a Mode of Protoplasmic Movement*, 9 J. EXPERIMENTAL ZOOLOGY 787 (1910).

33. See CREATING A TRADITION OF BIOMEDICAL RESEARCH: CONTRIBUTIONS TO THE HISTORY OF THE ROCKEFELLER UNIVERSITY 135-50 (Darwin H. Stapleton ed., 2004).

34. For the well-known history of blood transfusion, see SUSAN E. LEDERER, *FLESH AND BLOOD: ORGAN TRANSPLANTATION AND BLOOD TRANSFUSION IN TWENTIETH-CENTURY AMERICA*

transferring blood from one person to another cannot solve all problems, and it always carries risks, including potential rejection or infection.

Discovery is sometimes stimulated by crisis. In France in the 1950s, a serious radiation accident produced a number of victims with various forms of leukemia, a blood disease.³⁵ It was already known that blood cells arose in the bone marrow, apparently from hematopoietic stem cells. A flurry of research prompted by the French crisis led to discovery of the human leukocyte antigen that allowed the individual's body to distinguish between itself and other foreign cells and to initiate the body's effort to destroy the foreign invaders. How could medical science override the protective systems? By the 1960s, researchers conducted the first transplantation of bone marrow into a child with immunodeficiency disease, and the first marrow transplants on an unrelated patient occurred in 1973.³⁶

While these human success stories were remarkable, the major study of stem cells and their possibilities remained focused on mice. Mice are relatively easy to study, available from supply houses in genetically controlled lineages, and enough like humans to be a better model system than fruit flies, frogs, or nematode worms. In the 1970s Leroy Stevens was already following up earlier studies of abnormal developmental results such as teratomas. What caused such disorganized masses of "monstrous" cells in the mouse, he asked? If we could understand the cause of teratogenesis, we might begin to understand the causes of cancers and also the causes of normal differentiation.³⁷ During the next decades, many more researchers in a number of different labs took up mouse embryology, including a focus on the patterns of differentiation of embryonic stem cells.

Until the 1990s, the potential human applications of knowledge derived from mouse studies remained unclear. Embryonic stem cells were fascinating precisely because their fates were unknown and because they, in theory, had the capacity to differentiate into any and every separate kind of cell (though not necessarily in any organized way, and therefore, they are not totipotent and cannot become the whole). Yet because of this, they also could produce a tangle of wildly differentiated cells. Teratomas were common, for example, yielding a mix of teeth, hair, and other differentiated cells all jumbled together. Therefore, simply transplanting embryonic stem cells might well have yielded a muddle of cells

(2008); PBS, Red Gold: 1700-1919 Discovery and Exploration, <http://www.pbs.org/wnet/redgold/history/timeline3.html> (last visited Apr. 21, 2009).

35. MAIENSCHIN, *supra* note 21, at 252.

36. See, e.g., Cynthia M. Piccolo, Transplant Timeline – Bone Marrow Transplants, <http://www.medhunters.com/articles/transplantTimelineBMT.html> (last visited Apr. 21, 2009) (providing a history of bone marrow transplants).

37. See R. Lewis, *A Stem Cell Legacy: Leroy Stevens*, 14 SCIENTIST 19 (2000); cf. L.C. Stevens, *Teratogenesis and Spontaneous Parthenogenesis in Mice*, in THE DEVELOPMENTAL BIOLOGY OF REPRODUCTION 93 (Clement L. Markert & John Papaconstantinou eds., 1975).

rather than anything medically useful. Researchers were well aware of these limitations, and yet some persisted in developing embryonic stem cell lines in the hope that they would help us learn more about the nature of differentiation, and also because there was always the possibility that we could learn to engineer these cells to do what we wanted and to make them predictable.³⁸

This drive to understand and control differentiation is a basic foundation of medicine and applied biology. It is not new. As historian Philip Pauly brilliantly showed, in the late 1890s Jacques Loeb was already promoting a “mechanistic conception of life.”³⁹ Loeb produced parthenogenetic (asexual) sea urchins, eggs that divided and differentiated up to the pluteus larval stage. Loeb accidentally discovered that by changing the concentration of salt in the sea water, he could produce female sea urchins that did not need males to reproduce. The front pages of newspapers announced, “Science Nears the Secret of Life.”⁴⁰ If fertilization was not even necessary, and eggs could develop on their own, then females could produce their own offspring.

That was in 1899. The assumption was that with proper knowledge and techniques, scientists could control and engineer life processes. Today, scientists including Robert Lanza of Advanced Cell Technology reflect the same thinking.⁴¹ So do many of the scientists who led the advocacy march for funding for stem cell research in California and other states. If only we had money, they reasoned, we could take stem cell lines like those James Thomson produced in 1998, and we could get them to do what we want them to do. Then, since they would be differentiated according to our direction, we might assume that once a cell becomes a heart muscle (or brain or pancreas or whatever it is that we want) it will stay that sort of cell and function the way it is supposed to.

There is something exciting and high-minded about this view. In 1909, Loeb’s success brought considerable excitement and heavy financial support from the Rockefeller Institute.⁴² There was great hope for medical progress. And so we think today. But we should also be wiser now, over a century later. If we

38. See, e.g., M J. Evans & M.H. Kaufman, *Establishment in Culture of Pluripotential Cells from Mouse Embryos*, 292 NATURE 154 (1981); Gail R. Martin, *Isolation of a Pluripotent Cell Line from Early Mouse Embryos Cultured in Medium Conditioned by Teratocarcinoma Stem Cells*, 78 PROC. NAT’L ACAD. SCI. 7634 (1981).

39. PHILIP PAULY, CONTROLLING LIFE: JACQUES LOEB & THE ENGINEERING IDEAL IN BIOLOGY 130 (1987) (quoting PAUL DE KRUIF, THE SWEEPING WIND: A MEMOIR 42 (1962)); *id.* at 100. On this point, see Jane Maienschein, *Controlling Life: From Jacques Loeb to Regenerative Medicine*, J. HIST. BIOLOGY (forthcoming 2009).

40. See PAULY, *supra* note 39, at 218 n.31 (citing *Science Nears the Secret of Life*, CHI. SUNDAY TRIB., Nov. 19, 1899, at 33); *id.* at 100-02.

41. See Advanced Cell Technology, Fact Sheet, <http://www.advancedcell.com/fact-sheet> (last visited Apr. 21, 2009).

42. See PAULY, *supra* note 39, at 135-36.

are selecting cells precisely because they are pluripotent and capable of diverse differentiation, then assuming that we can cause them to differentiate exactly as they would normally involves assumptions more simplistic than those Ross Harrison made a century ago. Also, we are discovering with cloning and other related research that differentiation is not unidirectional. Indeed, some of the leading stem cell researchers talk freely about "resetting the developmental clock," "reprogramming," or "de-differentiating" cells.⁴³ Recently, several different laboratories have de-differentiated cells and reprogrammed them to act as if they were pluripotent stem cells.⁴⁴ If we can de-differentiate cells, then why do we assume that our engineering process will produce cell lines that, even once properly differentiated, will stay differentiated and continue to do what we want them to do?

Many questions remain, and they are wonderfully exciting questions that strike at the very heart of how development works. Researchers around the world are sharing some of their results (when not restricted by the intellectual property demands of private funding) and are benefiting from a major infusion of funding and attention to stem cell science as through the California Initiative funding.⁴⁵ What history shows us is that what we actually come to know and what we are able to do may be very different from what we expect. It may well turn out that pluripotent embryonic stem cell lines are useful for research now, but that what we really need are multipotent or unipotent precursor cells that are already partly differentiated. Perhaps these cells will be more likely to stay differentiated in the desired way once they are transplanted for use. We may come to appreciate the complexity of developmental responses to changing environmental conditions, tempering our genetic determinism with the gradual, epigenetic, development of differentiation and morphogenesis. Perhaps we can even learn that life is both more complex than simplistic genetic determinist views might have it, and more comprehensible and manageable than extreme epigenetic assumptions of complexity would demand. Just as Wheeler suggested over a century ago, wisdom may lie in seeking a middle ground, arriving at understanding not through philosophy and assumptions but through scientific exploration and evidence.⁴⁶

43. See, e.g., Nicole Rusk, *Resetting the Clock*, 3 NATURE METHODS 72 (2006).

44. See Keisuke Okita, Tomoko Ichisaka & Shinya Yamanaka, *Generation of Germline-Competent Induced Pluripotent Stem Cells*, 448 NATURE 313 (2007); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells*, 318 SCIENCE 1917 (2007).

45. See, e.g., California Institute for Regenerative Medicine, About CIRM, <http://www.cirm.ca.gov> (last visited Apr. 21, 2009).

46. See *supra* note 25 and accompanying text.

CONCLUSION

We see that it was largely because of exuberance for genetic determinism that we were surprised by cloning and then by stem cell research. We might have predicted these developments if we had had a more robust sense of the range of developmental possibilities and plasticities, and ideally even a sense of the history—both the history of science and the history of the complex developing organism. Instead, cloning and later stem cell research have created fears and worries about genetic duplication of persons. This fear hinges on the highly problematic assumption that a person is nothing more than the expression of the genetic complement.

Furthermore, public discussions have been distorted by more than the abortion debates, the absence of scientific knowledge, and the appeal to genetics experts as definitive sources of understanding; public debate has also been distorted by the bioethics industry. Well-meaning academics have been strongly supported for almost two decades by the Human Genome Project's ELSI program at NIH to study the implications of the genome project.⁴⁷ These academics are the experts to whom reporters and commentators turned for an ethical view of cloning and stem cell research.⁴⁸ Few were familiar with the developmental biology involved, and since they had been focused on and trained in other, largely genetic or general medical issues, they made mistakes about the science. Others have been exemplary in their caution, but nonetheless fall back on analogies to genetics. This case raises questions about who the experts should be in highly contested public discussions of science.

Surely, developmental biologists are relevant experts on the science involved. It is entirely appropriate to ask Ian Wilmut, James Thomson, Irving Weissman, George Daley, or Evan Snyder, for example, to explain their research. It is entirely appropriate even to ask what they see as the implications or possible applications, for example. It is even reasonable to ask them for their personal interpretations of what is at issue ethically; however, then they are offering just that—one individual's personal opinion. Bioethicists can also have individual personal opinions as well as professional analyses. Poets or engineers or schoolchildren may also have personal opinions, and only some are experts with respect to any particular question. Historians of science may even have opinions, including informed and helpful opinions. They may all have opinions about what is at issue, about values, and about proposed social actions. It is entirely appropriate, and indeed even necessary, that members of society individually and society as a whole have input into decisions about social actions, even those relating to the funding and regulation of science.

47. See National Human Genome Research Institute, ELSI Research Program, <http://www.genome.gov/10001618> (last visited Apr. 21, 2009).

48. See, e.g., COOK-DEEGAN, *supra* note 20.

What is not appropriate, however, is that social commentators *interpret* the science according to their own assumptions and values, and then present these interpretations as fact. Just as it is not appropriate for scientists to decide by themselves, on the basis of the science alone, what is moral or what ought to be legal, so it is not appropriate for citizens to decide by themselves, on the basis of their values alone, what scientific research is "moral," "good," or legally defensible.

In the heated and highly polarized political climate of the late twentieth and early twenty-first century, we have somehow allowed some particular groups to define the important questions what counts as scientific knowledge. In particular, the religiously-infused debates about abortion politics have been allowed to influence the discussion about embryo research far more than is warranted by the nature of the "expertise." Somehow, public debates about stem cell research have become debates about whether we want to save the pre-implantation embryos that these groups take as "persons" or whether we want to help save the lives and improve quality of lives for those suffering from degenerative diseases. These are the wrong questions, or at least they are not the only relevant and important questions. Let us start by asking about the empirical facts about developing embryos.⁴⁹

In particular, scientists show that at first an embryo *in vitro* is really a bunch of undifferentiated cells in a dish.⁵⁰ It would be scientifically unsound to insist that the earliest stage fertilized egg is biologically as developed as the later-stage fetus with all its body parts intact, including the beginnings of a beating heart and sensory system. Neurobiologist and member of the President's Council on Bioethics Michael Gazzaniga put it beautifully:

It is a truism that the blastocyst has the potential to be a human being. Yet at that stage of development it is simply a clump of cells. . . . An analogy might be what one sees when walking into a Home Depot. There are the parts and potential for at least 30 homes. But if there is a fire at Home Depot, the headline isn't 30 homes burn down. It's Home Depot burns down.⁵¹

Or as developmental biologist Lewis Wolpert has aptly explained, it is only with implantation and the stages after the blastocyst that biological differentiation starts to occur so that gastrulation (the point at which the germ layers first begin

49. See, e.g., Jane Maienschein et al., *The Ethos and Ethics of Translational Research*, 8 AM. J. BIOETHICS 48-49 (2008) (noting the "rush to translation" from fundamental stem cell research to clinical applications, which may "undercut[] [scientists'] abilities to study other kinds of fundamental developmental processes" and paradoxically hamper the lab science necessary for building therapeutic applications).

50. See Glenn McGee & Arthur L. Caplan, *What's in the Dish?*, HASTINGS CENTER REP., Mar.-Apr. 1999, at 36.

51. *Metaphor of the Week*, 295 SCIENCE 1637 (2002) (quoting Michael Gazzaniga).

to form) is “truly ‘the most important event of your life.’”⁵² Embryos go through developmental stages, as biologists have documented clearly for a century and a half, and each of those stages has a different biological “meaning.”

The earliest cell divisions are just that—divisions of material. It is as if we were cracking a glass window into a bunch of smaller pieces, but the whole hasn’t grown any larger. It’s now just a number of pieces rather than one unified part. Yes, these are still cells and they are “living” in some sense. But without any significant genetic action, and without any differentiation, they really do seem biologically to be “just” cells in a dish. To suggest that these are equivalent to a fully developed person is to devalue that person and the complex processes that have made him or her into the individualized self that results.

Cells divide and divide up to the eight cell stage, and as far as we can tell, in the earliest divisions there is no significant genetic action and no differentiation. This is why the eight cells are all totipotent, each capable of becoming an individual if separated from the rest of the cells. It is also why biologically we can remove one or two of the eight cells (which is sometimes done in fertility clinics for purposes of genetic testing) and the rest can still develop into a perfectly healthy baby.⁵³

It is also why we might be able to take one or two or even up to seven cells of the eight-cell stage and take them off to be developed to the blastocyst stage and then harvested for stem cells. We would still have the one individual person we would have had, without any loss of genetic information. But now we have seven stem cell lines all genetically alike. Such an approach might address some ethical concerns, since the one cell still becomes one individual organism with a particular genetic makeup; but now there are also extra cell lines with the same genetic makeup as well. Why not try it?

Developmental biologists might well ask such questions. The public might well ask such questions. Why not try such experiments? Why have we allowed those who are essentially genetic determinists and who insist that all stages of life are equally important to dominate the social and political discussion; why do we defer to those who refuse even to discuss more nuanced possibilities to define the terms of the debate? Partly, I suspect, this is because of the nature of the arguments about cloning, which created a focus on issues of “personhood.” And partly because of the history of bioethics as a field. Also, and perhaps most importantly, because too many biologists themselves have been seduced by

52. LEWIS WOLPERT, TRIUMPH OF THE EMBRYO 12 (1991).

53. There is some controversy about whether such preimplantation genetic diagnosis leads to problems or is a socially important tool. See, e.g., RUTH SCHWARTZ COWAN, HEREDITY AND HOPE: THE CASE FOR GENETIC SCREENING (2008); Stéphane Viville, Deborah Pergament & Morris Fiddler, *Ethical Perspectives and Regulation of Preimplantation Genetic Diagnostic Practice*, in PREIMPLANTATION GENETIC DIAGNOSIS 227 (Joyce C. Harper, Joy D.A. Delhanty & Alan H. Handyside eds., 2001).

genetic determinist thinking. They find it difficult now really to understand and to adopt the more epigenetically balanced understanding of development and differentiation that the science demands and from which the social needs might well benefit.

If we are all experts in some ways on these questions, let us assume our mantel of expertise wisely and seek to understand the full range of questions and possible interpretations. Let us work hard to identify and also to question our assumptions about development and its meanings. As Wheeler urged in 1899, let us work toward wise and balanced interpretations that respect as wide a range of views as possible without giving in to extremism on any side.⁵⁴

54. See Wheeler, *supra* note 25, at 216.