Chapter 12
History and Philosophy of Science at Work: Making Regenerative Medicine Research Better

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History and Philosophy have found various ways to be friends over the millennia, and so have History of Science and Philosophy of Science. History gives particulars that ground interpretations in stories and make them real. Philosophy gives analysis and connections to general themes that carry us beyond the particulars. Together, they offer perspective that can be more valuable and richer than either alone. Thus, it is hard to disagree with the claim that history and philosophy of science have much to offer each other.

Of course, there is also a tradition of philosophy and history of science pointing in different directions, drawing on different methodologies, and taking different measures of successful investigation. Historians tell stories, recount particulars of the individual episode before them, and often resist any efforts at generalization. What matters is people and places. Furthermore, in recent decades history of science as a field has been dominated increasingly by cultural history, where it is the context and culture that matter more than the science itself. Mere "internalists" who concentrate on the logic and methodology of science have been reviled. Meanwhile, philosophers have sought just the generalizations that some historians have rejected. They have examined just the internal logic and reasoning that some historians have eschewed in favor of contextualization.

Notwithstanding the tension that has appeared in diverse ways, some historians and philosophers have remained friends and have worked hard to overcome tensions and to draw on different methodologies and different values to achieve deeper and richer understanding of the nature and context of scientific practices. Despite disciplinary differences, historians and philosophers meet together in their annual professional meetings. An energetic group has organized a series of workshops on &HPS to integrate history and philosophy of science and promote the synergies. Collaboration and communication can work, and I offer a case study in favor of that claim.

Here I take a particular example and offer it as evidence in favor of the stronger claim that, in drawing on both history of science and philosophy of science together,

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it is possible to make science better. Making this case requires understanding what it means to assert that the science is better as well as how we can know. I do not pretend to have an argument completely worked out for this claim. Yet I propose that the particular example of regenerative medical research allows a strong demonstration that at the very least goes far toward making such an argument.

The discussion starts with a description of regenerative medical research today, and its context of claims that this is an exceptionally productive research field ripe for translation from bench to bedside and that it ought to be pursued energetically and with significant public investment. I discuss what is meant by regenerative research, by NIH's translational imperative, and by the political and ethical as well as scientific contexts in which this research exists.

The second section asks about the philosophical analysis of underlying assumptions of regenerative research, including metaphysical assumptions about what is being regenerated and epistemological assumptions about how we know what works. This section brings us discussion of form and function, preformation and epigenesis, determinism and adaptation, and wholes and parts. This philosophical analysis uncovers general themes and shows how they are playing out in this particular case. Philosophical inquiry brings analysis and reflection to the often and perhaps necessarily over-enthusiastic presentation of the research. As a result, we see that researchers are making several assumptions that are limiting the scope of their research and have pointed the research in limited directions while missing others that might be at least as productive.

Third comes an exploration of the lines of research that have led to regenerative research today. This historical tracing of particulars shows a number of research questions and approaches that were set aside, not understood, or otherwise ignored or lost to current researchers. There is value in recovering them. We can learn from examining paths not taken or ways of working long cast off. And we can gain a much wider and richer picture of the research today by placing it in historical context.

Finally comes the section addressing the "so what" questions about any project: so what if scientists today ignore history and philosophy? So what if they could learn more through this study; do they really need to? Well, no, it is certainly not necessary that each scientist study history and/or philosophy. But I argue that history and philosophy can nonetheless make science better as a whole. The task here is to show what such a claim might mean and in what sense it might be true.

12.1 Regenerative Research: The Science in Context

"Regenerative medicine" covers a diversity of research approaches, but the term has been shaped by the National Institutes of Health and leading institutes in the U.S. and elsewhere. The Whitehead Institute in Cambridge, Massachusetts, gives a widely-shared definition: "Regenerative medicine: Seeks to understand how and why stem cells, whether derived from human embryos or adult tissues, are able to develop into specialized tissues, and seeks to harness this potential for tissue-replacement therapies that will restore lost function in damaged organs" (see Whitehead 2008). Irving Weissman's Institute for Stem Cell Biology and

Regenerative Medicine has a similar focus, so that his team feels that "The Stanford Stem Cell Biology and Regenerative Medicine Institute is at the forefront of a groundbreaking approach to biomedical research and patient care. This approach aims to harness the power of stem cells—master cells from which all specialized cells and tissues in our bodies are derived—to target and remedy the root causes of today's most devastating diseases" (Stanford 2008). In fact, the entire California Institute for Regenerative Medicine makes clear that their mandate is to promote and develop stem cell research (CIRM 2008) .

All these institutes, and nearly all of the many, many others with those words in their names, emphasize the goal of drawing on stem cell technologies to restore function for clinical purposes. A few also mention regeneration of structures, in order to recover lost function, but the focus remains on function and is nearly always stated in terms of clinical application, even when the research being carried out includes basic developmental biology and related fields.

Amidst the vast number of research publications and polemics available, two summary sources are particularly helpful in providing insight into how researchers see the field developing. The first is the NIH report "Regenerative Medicine 2006." This 65-page compilation of six chapters summarizes work on embryonic stem cells, bone marrow stem cells, nervous system repair with stem cells, genetically modified stem cell experimental therapies, and intellectual property issues surrounding stem cell research. A 2007 addition entitled "Mending a Broken Heart" addresses stem cells in cardiac repair. Each chapter offers an overview of the dominant research areas and the implications for regenerative research agenda, which very much reflects NIH priorities at the time (NIH 2006).

Notice that the report is entitled "Regenerative Medicine" and that every chapter concerns stem cell research. It follows the 2001 report on "Stem Cells and the Future of Regenerative Medicine" (NIH 2001) and reflects NIH packaging of stem cell research in terms of regeneration and the other way around. We see a similar pattern in California's Proposition 71 and its implementation. Regenerative medicine can surely be more than stem cell research, but they have become linked and nearly synonymous for some purposes and contexts. It is worth understanding why. Similarly, stem cell research is about far more than just regenerating function but has gotten packaged as applied regenerative research for clinical purposes. Again, it is worth understanding why. And it is not enough to say knowingly, "Ah, it's political." We need a better sense of the research and the political climate including a look at NIH and research funding, at public expectations of publicly-funded science and the scientific community's expectations for their research, and of the stem cell research and regenerative applications actually being carried out. Let us take each in turn.

12.2 NIH Mandate

The National Institute (at first just singular) of Health began in 1930 with the Ransdell Act. A mix of advocates argued that the U.S. Congress needed to take responsibility and fund research leading to health improvements. They began

targeting specific diseases, which led to multiple institutes, each for a favorite disease that has gained sufficient advocacy (see Starr 1982).

The NIH mission has remained focused on health. Since 2002 it has also emphasized translational research, dedicated to "translating" scientific research carried out at the laboratory benchside into clinical applications at the bedside. In response to political pressure to make the applications more quickly and more visibly, the new NIH Director Elias Zerhouni developed a "roadmap" to facilitate translation (NIH 2008; see Maienschein et al. 2008). The agency also began funding Clinical and Translational Science Centers (CTSCs) and a number of targeted major projects.

Yet the precise expectations and interpretations remain unclear. As Declan Butler suggests: "Ask ten people what translational research means and you're likely to get ten different answers." Butler points to the new rhetoric as beginning with the first appearance of the term "translational research" in PubMed in 1993, following research on the BRCA1 and other cancer genes (Butler 2008, 841).

The push for translation arose from opportunity as the genome project produced new knowledge apparently available for application and public demand for health results. Zerhouni felt that "There was a widening gap between basic and clinical research" that needed to be addressed. An unsigned editorial in *Nature* agrees that this is still true, acknowledging that "Some researchers complain that an emphasis on translation swings the pendulum too far towards applied science at the expense of basic research, but this concern has little foundation. In fact, what is worrying is the extent to which biomedicine in the past few decades has swung so far toward pure science" (Editor 2008).

Stem cell research, with its public promises of significant clinical applicability, has become a poster child for translational research. The slogan "regenerative medicine" works well for public interests, NIH translational needs, and a growing research community's interests. This is particularly ironic, since the specific research area that many consider most promising uses human embryonic stem cells and is currently limited by President George W. Bush's Executive Order on August 9, 2001 restricting use of federal funds for just that research (White House 2001). Regenerative medicine, translational imperative, and stem cell research are all tied together by the accidents of history and politics (see Maienschein et al. 2008).

California gives us a site where the intersection has played out most forcefully and to greatest immediate effect. Proposition 71, passed by the state's voters in November 2004 and signed into law by a supportive Republican Governor Arnold Schwarzenegger, led to the establishment of the California Institute for Regenerative Medicine (CIRM). The proposition emphasized stem cell research in particular. The campaign was well documented, especially by the *Washington Post, New York Times, Science* and *Nature*, and brought a parade of Nobel Prize winners and Hollywood celebrities to endorse the call for publicly-funded stem cell research. The packaging in newspaper and television ads emphasized the treatments that would result and directly linked stem cell research to predicted clinical results. Bills in the U.S. Congress were first oriented toward opposing such research and especially cloning, but shifted to supporting stem cell research by 2005. The Stem

Cell Research Enhancement Acts explicitly to allow such research did pass in 2006 and 2007, but President Bush vetoed—the first veto of his presidency.

The stage was set for a program of regenerative medical research in the twenty-first century, with broad support from the public and the scientific community. Such research is being done energetically in California and some other states, by privately funded research institutes, and especially in other countries that have not had the same ethical and political debates as the U.S. Many researchers report that a rising percentage of publications of stem cell research are coming from countries other than the U.S., including some that have invested heavily in this area (Owens-Smith and McCormick 2006).

12.3 Expectations of Science

It is worth a brief reflection on the social contract concerning science and the implications for regenerative medicine. There is little point in rehearsing the well-worn paths of bioethics and policy debates, but there are other relevant factors shaping the scientific context and therefore the science. One of these concerns what the public expects of science. Clearly when the NIH was established, Congress and the public supporters expected research and results that would improve health and cure disease. The National Science Foundation was established in 1950, with the mission "to ensure that the United States maintains leadership in scientific discovery and the development of new technologies." As Vannevar Bush proposed, NSF would pursue new knowledge that would lead to useful results someday in some way, while the NIH was expected to focus on solving disease problems (Bush 1945).

The current push for translation and particularly for regenerative medicine puts a greater emphasis on outcomes—often particular defined outcomes and preferably achieved quickly. The public voting for the California initiative wanted not some vague promises or future applications, but to cure Parkinson's disease and diabetes, among others. They wanted researchers to engineer stem cells to regenerate particular lost functions. A clearly desirable goal, this strong direction for research may nonetheless not suit the way scientific research institutions work best and it may distort the types of research done. While this distortion may be a good thing in some ways, it clearly shifts the emphasis and ways of working.

In the short run, the focus on results of particular kinds benefits established researchers already working on stem cell science. Yet many of these researchers are excellent developmental biologists with strong track records who were working on other problems. It remains to be seen whether, how, and to what extent the current demand for results of particular kinds impacts the research enterprise beyond adding lots of funding to new directions. It also remains to be seen how the public reacts when it becomes clear that researchers are not able to deliver on all the promises made during political campaigns. The scientific community is surely already making wonderful discoveries, but just as surely many will be surprising and not the outcomes that had been predicted. We may not figure out ways to get stem cells to produce dopamine neurons in the brain to repair Parkinson's losses, for example,

but we may be able to engineer cells to prevent or control the disease in other ways before it does the damage. Researchers—and the entire research network—are likely to deliver on the loosely understood social contract that public investment will produce some clinical results. Those just may not be the particular results that the public campaign emphasized and that the public supporters imagined.

12.4 Stem Cell Research and Regenerative Applications

So where are we with regenerative medicine? The NIH website does a good job of updating research statutes and pointing to work from within and outside the NIH. The individual institutes do an excellent job of presenting their research programs and the results that have been published. Not surprisingly, they do less presentation of research in progress or research results that have likely significant proprietary value that they (and their funders) want to protect.

The 2006 NIH report provides a useful survey, and it is worth noting the precise message delivered and the particular language chosen. Like most discussions of regenerative medicine, it starts with Prometheus. Chained to a rock, this mythical Greek spends every day with an eagle eating his liver. Yet every night the liver regenerates, "enabling him to survive." Furthermore, as the introduction to the NIH report puts it, "The scientific researchers and medical doctors of today hope to make the legendary concept of regeneration into reality by developing therapies to restore lost, damaged, or aging cells and tissues in the human body" (NIH 2006, i). This interpretation of the myth is instructive. Usually, the tale is presented in terms of the punishment of Prometheus for his having given fire to humans. As a result, he must endure having his liver eaten again and again, suffering for his act. Yet here, we get an uplifting tale: look, livers can regenerate, and today's researchers can help make this happen. Isn't this great! The interpretation tells us much about the optimistic expectations for regenerative medicine even when, as the report makes clear, very few clinical applications have yet been established.

The first full chapter of the report on regenerative medicine is entitled "Embryonic Stem Cells" and spells out what they are, what they can do, how they are most effectively cultured (growing best in media that have proven problematic for human clinical use), why pluripotency is so desirable but potentially problematic, and possibilities for genetic manipulation. This sets the stage for more clinically applied work.

Chapter 2 discusses hematopoietic stem cells from bone marrow. The essay points to the post WWII attempts to restore blood supplies to patients with leukemia and other diseases resulting from irradiation. Hematopoietic stem cells are the only stem cells known to provide consistent stem cell therapy, having been used and their efficacy proven since 1959 as clinical transplantation. This is a case of taking cells that are already somewhat differentiated and known to give rise reliably to blood cells and transplanting them to a patient. Translation starts with transplantation in this case, and the history of transplantation research from developmental biology interests with the clinical applications in ways to which we will return. This

is also a case of transplanting "adult" stem cells, meaning cells taken from older-than-embryonic stages. This chapter, by Jos Domen, Amy Wagers, and Irving L. Weissman, concludes with a realistic assessment of the challenges as well as hopes that "After more than 50 years of research and clinical use, hematopoietic stem cells have become the best-studied stem cells and, more importantly, hematopoietic stem cells have seen widespread clinical use. Yet the study of HSCs remains active and continues to advance very rapidly. Fueled by new basic research and clinical discoveries, HSCs hold promise for such purposes as treating autoimmunity, generating tolerance for solid organ transplants, and cancer therapy. However, many challenges remain" (Domen et al. 2006, 28). The 180 papers cited give ample indication of activity in this research field.

Chapter 3, by David Panchision, looks at research on nervous system repair. Quite a number of diseases and conditions would benefit from regeneration of neural function. Until the 1990s, it was generally assumed that nerve cells stop developing in adults, so that the best hope was in limiting damage or retaining existing neural networks. Then it became clear that at least some neurons differentiate in adults, perhaps from residual stem cells. "These findings are exciting because they suggest that the brain may contain a built-in mechanism to repair itself. Unfortunately, these new neurons are only generated in a few sites in the brain and turn into only a few specialized types of nerve cells. Although there are many different neuronal cell types in the brain, we are now optimistic that these new neurons can 'plug in' correctly to assist brain function." These findings give increased hopes for getting cells to do what is needed for degenerative diseases. "For this reason, a huge effort is underway to develop new treatments, including growth factors that help the remaining dopamine neurons survive and transplantation procedures to replace those that have died." But we should not do just any research at any cost. Rather, "it is the current task of scientists to bring these methods from the laboratory bench to the clinic in a scientifically sound and ethically acceptable fashion" (Panchision 2006, 35, 37, 42).

Chapter 4 looks at gene therapy as related to stem cell research, especially using stem cells as a vehicle for such genetic manipulation. Chapter 5 addresses Intellectual Property issues, especially given the international nature of the research and the complexities of funding.

Chapter 6 was added in 2007 and looks at cardiac repair. Though diseases gain great attention with poster cases like Parkinson's Michael J. Fox or spinal cord injury's Christopher Reeve, or with poignant stories such as the degeneration of Alzheimer's or the failed insulin function of juvenile diabetes, in fact heart disease is the most common in the U.S. and many other countries. Cardiac disease is the number one cause of death in the U.S. and apparently has been in every year starting in 1900 with the exception of 1918, where influenza surpassed it.

Researchers are exploring diverse ways to repair heart muscle cells, and so far heart transplantations have been the most successful of regenerative approaches—in the few cases where hearts are available for transplant and not rejected. Some trials with transplanted cells, including myocardial progenitor stem cells, seemed to lead to differentiation into heart cells of several types. Yet it now seems more likely that "transplanted stem cells release growth factors and other molecules that

promote blood vessel formation (angiogenesis) or stimulate 'resident' cardiac stem cells to repair damage. Additional mechanisms for stem-cell mediated heart repair, including strengthening of the post-infarct scar and the fusion of donor cells with host cardiomyocytes, have also been proposed" (Goldthwaite 2006, 58).

Whatever the mechanism, a major remaining challenge is getting the cells delivered to the functional site, and another is timing the cell delivery effectively. For cardiac repair, experimentation on multipotent or progenitor adult stem cells may hold at least as much promise as with pluripotent embryonic stem cells. Indeed, using such adult cells may avoid some of the risks of teratoma formation and other problems of undifferentiated pluripotent cells that have too much potency. So while such research holds great promise, "the use of these cells in this setting is currently in its infancy—much remains to be learned about the mechanisms by which stem cells repair and regenerate myocardium, the optimal cell types and modes of their delivery, and the safety issues that will accompany their use. As the results of large-scale clinical trials become available, researchers will begin to identify ways to standardize and optimize the use of these cells, thereby providing clinicians with powerful tools to mend a broken heart" (63).

What we learn from the report as a whole is that all of stem cell research is just beginning. While we have a half century of experience with hematopoietic stem cell transplants, decades of study of mouse stem cells, and several decades of experience with a select handful of organ transplants, we have actually made tremendous progress in understanding more and more details of developmental biology but not much progress with clinical applications—not yet. And what we have learned has often challenged or contradicted previous assumptions, as we will consider in the next sections.

Another more recent set of publications appeared May 15, 2008 in *Nature*. Intended for an audience of researchers, these reports are more technical and detailed, but they also show that progress is occurring quickly on many fronts. One area of considerable promise concerns induced pluripotent stem (iPS) cell lines. Here we see changing assumptions. Early stem cell research focused on being able to take embryonic stem cells from blastomeres, because these were the ones that exhibited pluripotency, and culture them in such ways that the particular culture medium determined what kinds of cells they become. But considerable study of developmental processes and how growth factors shape differentiation has begun to show how already differentiated cells can be re-differentiated and even act (at least as far as researchers can tell) very much (though not precisely) like pluripotent embryonic stem cells. This is tremendously exciting research because it may reduce the need for embryonic cells and it shows a great deal about the complex of factors that shape development (Zon 2008, 311).

What had been called "cell fate" and "determination" has now been joined by ideas of "differentiation," "de-differentiation," "redifferentiation," and "reprogramming." Development is once again an exciting dynamic process, as it was around the early twentieth century, rather than a matter of playing out inherited deterministic preformationist programs. This trend is good for biology.

Language matters in all this flux of discussion—and especially as researchers and different areas at the bench, the bedside, and in the public try to communicate

effectively and reliably. It is hard, for example, to get away from the idea of cells as being programmed. Senior editor Natalie DeWitt, in introducing the section on regenerative medicine, starts her column by invoking regeneration: "Although some of our cells have the innate ability to replenish themselves—and, by doing so, to repair ageing and injured tissues and organs—most of the body's cells form the specialized cell type they are destined for and then go into lock down." She then moves to "the field of programming" which she locates as beginning with John Gurdon's work on frog cloning by nuclear transplantation from early somatic cells. Then a paragraph on Prometheus and creation as scientists discover "how to create new sources of such cells in a Petri dish." The last paragraph is virtually a statement of the NIH translational mission: "The articles in this Insight explore the promises and challenges of the next era of regenerative medicine—and how to use the information gained from the study of model organisms and cell culture to eventually heal" (DeWitt 2008).

In the fifty rich pages that follow, we learn about such research as cell therapies, molecular pathways, variability even within cell lines, specific genetic factors and knock out-knock in technologies, and what is meant by self-renewal of embryonic cells. Some of the work thought to be relevant is about regeneration, other research is about generation gone wrong with production of teratomas and immune system reactions/rejections. We learn about successes with adult cells that are not de-differentiated or re-differentiated by rather caused to differentiate in ways other than expected. To move to clinical successes, however, we will need to establish definitively both that the cells targeted are actually causing the effects claimed and that they do so in stable and predictable ways.

We see a diversity of approaches that involve basic developmental biology carried out in the lab. Researchers have to get stem cells, isolate and culture them, then make them do what is wanted, sometimes with genetic modifications. Transcription and growth factors are critical to facilitate differentiation of the "right" sort. Researchers internationally are busily studying all aspects of these processes, in humans, mice, and other organisms. And the NIH provides a valuable summary of current research at http://stemcells.nih.gov/research/current.asp, while other countries and institutes provide their own summaries.

The science in these papers is tremendously exciting, both for the promises of possible clinical applications and for its direct emphasis on what we learn about development and the basic research before clinical applications are in sight. Assumptions are shifting, and researchers are acknowledging that differentiation is much more complex and fascinating than the impression given in the public debates about California's research initiative or proposed Congressional legislation.

12.5 Philosophical Analysis

Given the burgeoning body of research and ambitions for medical applications, what can we learn by bringing the tools of philosophical analysis to bear? For our purposes here, I will set aside the vast bioethics discussion of stem cell research and its social and policy contexts. With some notable exceptions, this discussion has

been rather myopically focused on a few standard issues and has started with basic assumptions that are highly contested. Unfortunately, only a few of those eager to enter debates about stem cell research have made serious attempts to understand deeply the science involved. Instead, they have latched on to well-worn issues of personhood, identity and autonomy, and worries about whether people should be allowed to donate or even sell eggs or embryos for research or whether that constitutes exploitation. Fortunately, a few scholars have taken up more challenging and new issues, such as the moral and scientific status of chimeras or the implications of induced Pluripotent Stem Cell research (Robert and Baylis 2003; Robert 2004a; Robert 2006).

Let us begin here by recognizing that stem cell research already exists—on embryonic stem cells from human blastocysts and a range of stem cells from other sources. Let us acknowledge that the work is both possible and that some researchers are already experimenting with such things as chimeras made up of cells from more than one individual and even more than one species. Whatever the moral status, the science of regenerative medicine is underway in the U.S. and perhaps especially elsewhere. We are already repairing and replacing cells and tissues in a diversity of ways. Let us then turn to analyzing the work and let others debate the ethics and policy and make the laws.

Philosophical analysis is useful because it allows us to ask some of the questions that researchers are not asking. In some cases, it just has not occurred to them to ask and in other cases the underlying assumptions are so strong that the answers seem clear. Let us focus on four sets of questions to get at different parts of stem cell research. In each case, I will examine the driving questions and assumptions, and will also challenge existing views where appropriate. Key areas of interest focus around:

1. Metaphysical issues. What are stem cells, and how do they work? Is there, for example, such a thing as "stemness" and if so what is it and what does it do? What do toti-, pluri-, multi-, and uni-potency and progenitor status mean? This leads to other questions, such as whether if stem cells are the sources of new cells in the body, then does manipulating stem cells change the autonomy or identity of that body?
2. What does "regenerative" really mean? Does something become regenerative because it actually regenerates—and in what sense? Regeneration of the same part, of the same function, or of some replacement function that "works" even if in a different way? Does regenerative medicine involve repair of structure or function—or replacement with some others? And how—through genetic engineering, injection, transplantation? By causing new differentiation of something previously undifferentiated, or de-differentiated and re-differentiated? Is programming involved—necessarily?
3. Epistemologically, what counts as an explanation of the regenerative phenomena? Does regenerative success result from the presence of particular genes, transcription factors, function, assumptions about stemness, or what? How do we demonstrate/confirm such claims?

4. And how can we develop new knowledge when we cannot directly observe the regenerative processes? What role do assumptions about model systems play, or about the behavior of cells as they are necessarily transplanted from in vitro to in vivo settings?

In the end, we see that the research community is making a number of assumptions that may be wrong. It matters because putting wrong cells in the wrong places or in such a way that they start to do wrong things could be doing degenerative rather than regenerative medicine. Obviously that would be problematic. In more detail, then:

1. What are stem cells and how do they work? Immediately after James Thomson and John Gearhart brought human stem cells to public attention in 1998, numerous versions of definitions arose. Stem cells are those that both remain undifferentiated and also retain their capacity for self-renewal. Stem cells are never totipotent, meaning that they never have the capacity to become an entire organism. They can be—as embryonic stem cells taken from blastocysts distinctly are—pluripotent, meaning that they have the capacity to become any kind of cell. At least that's the assumption.

In fact, there is not any way to prove absolutely that any given cell or even group of cells has this capacity to become any from among all the possible kinds of cells. Here is one assumption already worth uncovering and examining. Perhaps there are factors making some stem cells from the same cell line pluripotent and others only multipotent, that is capable of becoming any of several but not any from among all the types of cells. Perhaps all the cells in the same cell line cultures in the same medium and derived from the same blastocyst are not, in fact, the same. This would be very valuable to know, in which case more detailed studies of the nature, causes, and effects of the diversity would be potentially useful. In fact, there is growing evidence of such differences.

Multipotent or unipotent stem cells are self defined, and progenitor stem cells seem equally so, in that they are apparently destined to become a particular kind of cell for which they are the progenitors. But what makes a cell determined enough to count as a progenitor but not differentiated enough to count as a whatever-type-it-is-cell already? Considerable work is being done on developmental regulators and factors allowing self-renewal or guiding differentiation (for example, see Zon 2008, 308).

Early assumptions still very much adopted a traditional view of development that the arrow of differentiation goes in only one direction, and that genetic control (or programming) with some input from environmental signals shapes the nature and tempo of the differentiation process. Recent accumulating evidence challenges that assumption and suggests that "reprogramming" is not just a rarity brought about by such interventions as cloning technology. Such reprogramming, de-differentiation or already differentiated cells, and re-differentiation based on new conditions seem to happen much more commonly than thought until quite recently (Robert et al. 2006).

Philosophers would find it easy to say something like "well, we could have told you scientists to question your deterministic assumptions." Hindsight is easy. What

do we have to add now? First, what do we gain—and lose—by holding so tightly to the programming metaphor? And also what is gained—and lost—by imagining a developmental arrow in only one direction, or by thinking in terms of single cells and their particular environments rather than more complex systems?

Perhaps normal development involves something that acts functionally like programming, with information sources captured somewhere in the DNA and/or the material biochemical structure of the embryo and subsequent developmental stages. Perhaps when cells are taken out of context, whether when pluripotent embryonic stem cells are removed from a blastocyst or adult stem cells from bone marrow, perhaps their entire functioning is reset. Perhaps they are no longer "programmed" at all (if they ever really were). Perhaps we should expect rather than be surprised if cells that apparently are the same behave differently, because just perhaps they are not really programmed in any very deterministic way. Perhaps they are responding much more to environmental cues or to signaling among cells and the surrounding medium than we thought possible. Furthermore, perhaps the arrows of differentiation flow both ways—or many ways, with more and less differentiation at different points in the cycles of cell division (as seems likely) or different densities of cells—but in deterministic ways. Perhaps individual cells have "minds" of their own and can "choose" different behavior and developmental pathways based on random choice, availability of necessary growth factors, or relationships with neighbors.

It could be quite useful to take up theoretical developmental biology that draws on new metaphors, explores new ways of thinking about the "social" interactions among cells, and looks beyond genetic transcription factors to include other environmental conditions. For example, Jason Scott Robert has articulated a vision of creativity in development that is directly on point here (Robert 2004b). He theorizes that from a single-cell stage, organisms adopt, construct, process, and regulate developmental resources of various sorts dispersed throughout the organism and its environment. Accordingly, development is a semi-autonomous, creative, self-constitutive process engaged in by the developing organism. Perhaps past evolutionary adaptations to changing conditions are relevant. Scott Gilbert's call for a robust ecological evolutionary developmental biology (or eco-evo-devo) sounds compelling here. Such dynamics systems approach might prove informative for explaining why hematopoietic transplants work something and not others, or why some cells become self-replicating and cancerous in some contexts and not others (Gilbert 2001).

One question remains that philosophers like to worry about and biologists usually do not, but that might matter here. What if a patient develops diabetes and we replace the function that produces insulin; then he develops leukemia and we replace the bone marrow and hence introduce new hematopoietic stem cells; then he develops cardiac disease and we replace multiple kinds of heart muscle cells or even the heart itself. Then brain cells with dopamine-producing neurons to control Parkinson's, and so on. As with the philosophers' concern about Aristotle's ship in which each part is replaced with new parts, we ask about identity: is it the same person after all those changes? What if the stem cell parts come from other individuals and carry different genetic materials, and hence make the resulting individual a

genetic chimera: does that matter? Is this the same person? What if we genetically engineered stem cells: would that make a difference?

Is there a point at which regenerative medicine goes so far that it is more generative of something new and different than regenerative of something that already exists and just needed repair? If there is such a point, where is it—and how do we know? And does it matter? Such questions hold philosophic interest, certainly, but they also raise the serious possibility that perhaps not all medical intervention is desirable for practical as well as moral reasons. If we change enough, with or without genetic engineering, do we make the new whole unable to function "properly"?—or in a way that we consider a successful medical result? This is not just an ideal abstract and not just an ethical question.

2. Related to the last concern is the broader question what we mean by "regenerative." The term suggests regeneration, which suggests re-generating of something. That is one interpretation, and some of the stem cell research is oriented toward the goal of regenerating lost function (getting cells in the right place to do the right thing) and in some cases lost function and structure. Regenerative medicine includes more than this, though, as with hematopoietic stem cells that may produce new blood cells but in different combinations than the original and may get more or different capacities than they had before. Or even further there are examples of repair of damaged cells with something different—skin that is scarred but covers the wound, for example. Or engineered prostheses to replace function in different ways than the original, such as a wheelchair or pacemaker in the heart or shunts to reduce pressure in the brain. Transplantation, starting with heart, skin, and bone marrow transplants, have had the longest history of success but also limitations that have proven instructive. It remains to be seen how other forms of replacement, repair, or regeneration will work.

3. Epistemologically, what counts as an explanation of regenerative phenomena, and how can we demonstrate this? This is a very difficult question that has few definitive answers as yet, though it is becoming clear that a mix of genes, transcription factors, growth factors, environmental stimuli, and interactions with other cells are all relevant. All contribute to causing differentiation to go as it does. And it requires a complex interactive systems theory to explain how and why the various causal factors interact (Robert et al. 2006).

One challenge is testing a theory. Even where it is clear that particular factors like presence of a transcription factor are associated with an effect, and even where the effect did not occur before and does now, this does not give a very robust causal explanation. Yes, that factor may have been a necessary but probably not a sufficient condition. Causation is often difficult to demonstrate, of course, but this is a case where each cell line is different and perhaps even individual cells within the same lines are different because of interactions with the other cells. To some extent, cultures of exactly defined conditions yield similar-seeming cells. But when they are transplanted into different environments, it is very difficult to establish which factors made a difference.

4. Part of the problem is inability to observe directly the regenerative process. We can see cells in a dish, but only indirectly the results when they are transplanted to a new site to produce regenerative results. And in the new setting, cardiac cells may seem to produce beats like myocardium is supposed to—but how can we tell? How can we tell epistemologically? And how can we even do the research in humans that would require transplanting cells into patients when we have no way of determining the safety or efficacy of such a transplantation before we try it? We can test in animal models, as usual in medicine, but one of the things we know clearly is that stem cells develop differently in different environments (which is, after all, why we value them—we believe that we can cause them to differentiate in defined desired ways by culturing them in particular ways). Therefore, we should expect that these cells in animal models will precisely NOT behave as they would in humans. The animals therefore do NOT serve as very useful models for purposes of stem cell research (Robert 2004a, b; see Robert et al. 2006).

We are left with ethical concerns about the extent to which we are comfortable creating chimeras of human and animal cells, but equally challenging are the epistemological barriers. Researchers can begin to address them, but only by carrying out a great deal of fundamental work in developmental, cell, and molecular biology. Much of this work holds little immediate promise of translation. And much will require exploring creative new theoretical approaches to complex systems and getting well beyond metaphors and deeply-engrained assumptions about programming and uni-directional differentiation.

12.6 History of Regeneration Research: Tangled Threads

Regenerative medicine has grown out of many different lines of research, addressing different questions with different methods and approaches and with different goals in mind. Alejandro Sanchez-Alvarado provides a nice introductory lecture from the perspective of a current leading research on regeneration (Sanchez-Alvarado 2008). I likewise find a rich set of traditions informing research today. It is worth looking at some of those (see Maienschein 2009, for more detailed discussion).

Arguably, the first true stem cell research in the modern sense was Ross Granville Harrison's experiment on nerve fiber development (Harrison 1907). Harrison's particular interest was in nerve development. He wanted to show how nerve fibers grow and hypothesized that they reach out by protoplasmic outgrowth. He denied the alternative popular view that organisms develop their nervous systems because of preformed bridges. For Harrison, arguing and pointing to more and more beautiful silver nitrate solutions like those of Camillo Golgi or Santiago Ramon y Cajal would not settle the question.

Harrison sought to do that definitive settling of the question with a crucial experiment. He cut neuroblast cells (neural stem cells) out of the frog and placed them into an artificial culture medium, in this case a hanging drop of frog lymph. Out grew a beautiful nerve fiber, just as in the case of normally developing frog nerve fibers. The experiment had answered the question about development, had produced the first successful tissue culture ever, and had (in retrospect) demonstrated the capacity

of neural stem cells to differentiate in an artificial medium. The work began while Harrison was at the Johns Hopkins University and continued after he moved to Yale in 1907. There, under the influence of bacteriologists, he refined the methods and achieved even greater success with his cultures (Maienschein 1991).

Harrison moved on to other questions about embryology and left it to others such as Alexis Carrel at the Rockefeller Institute to carry tissue culture to new applications and to clinical translations (Landecker 2007; Stapleton 2004). Meanwhile, other researchers looked at the biological phenomena of regeneration. Thomas Hunt Morgan was one of those, whose 1901 book *Regeneration* provided a summary of centuries of work to that point. Morgan's 316 pages described the experimental and theoretical studies of regeneration, beginning with a retrospective review of earlier studies on a diversity of organisms such as hydra, worms, frogs, and planarians. The book grew out of a series of lectures presented at Columbia University, where Morgan was a faculty member. And they drew on his earliest reflections presented in a lecture at the Marine Biological Laboratory in Woods Hole (Sunderland 2007; Morgan 1901).

Morgan had come to see regeneration as a way to understand normal development but also reflecting special circumstances and in some cases special capacities. Regeneration was, in many ways, a problem of growth and replacement of material form that took place with the guidance of "tensions" within the organism itself.

Lewis Wolpert analyzes Morgan's "ambivalence" reflected in his tensions hypothesis and notes that at times Morgan's interpretation seems very like the gradient theory of Charles Manning Child, which Wolpert himself favors. At times, Morgan seemed to embrace gradients and rely on them to explain polarity and other phenomena. Yet at other times, Morgan reverted to alternative accounts. As Wolpert notes, Child's own views are very difficult to understand at times, so it is perhaps not surprising that Morgan and his contemporaries largely ignored Child and his extensive studies of planarians and gradients (Wolpert 1991; Mitman and Fausto-Sterling 1992). At that time, neither gradients nor tensions provided much of a tractable research program for getting at how either gradients or tensions actually work or what causes them. Saying that gradients cause regeneration but that we have no idea how gradients are established does not get us very far, as Morgan explained.

Another important line of research that led to what was considered an embryological "gold rush" came in the 1920s and concerned "induction" and the role of what Hans Spemann identified as the "organizer." Could it be that whatever chemical forces and factors cause induction are causing differentiation and therefore generation? This was an obvious question, but the researchers most focused on studying induction saw normal development and differentiation as the real prize. Regeneration was a curious phenomenon, yes, but it was not clear how planarians or earthworms or hydra generating missing parts of themselves would reveal much about normal development. Re-generation might well be different processes or depend on different causes than induction and generation in normal development.

One line of research pursued especially by Harrison, Spemann, and their many students involved transplanting all sorts of frog parts: limb buds and eye vesicles, and also bits of "organizer" material from the dorsal lip of the blastopore. Or they tried other non-frog and non-organic materials to see which ones induced

differentiation and how. Still others transplanted nuclei into egg cells, leading to Robert Briggs' and Thomas King's cloning of frog's eggs in 1951 and John Gurdon's later demonstration that even later developmental stages could be cloned. Transplantation and cloning raised serious questions about the capacities and limits of cells to become dedifferentiated, redifferentiated, and differently differentiated, for example. Underlying assumptions about what was possible and not possible kept researchers from pushing further in the direction of cloning later stage or somatic cells, and it is intriguing to reflect on why those assumptions were made (see Maienschein 2003).

After spending decades studying genetics in fruitflies and winning a Nobel Prize, Morgan returned to regeneration as a foundational problem in embryology. It became clear that he had never really given up his fascination with regeneration. In *Embryology and Genetics* in 1934, he noted there are really two different forms of regeneration. "In one the new structure develops by a remodeling of the old materials; in the other the new structures are formed out of new materials that are derived from the old part" (Morgan 1934, 164). Morgan was well aware that "location" may be everything, but that merely invoking it explains nothing. Perhaps the new cells contact with other cells and there is some physical or chemical influence, or perhaps the old cells act as "determiners" or "organizers" for the new cells.

Others have taken a more theoretical rather than experimental approach. Paul Weiss, for example, asserted in his 1939 *Principles of Development* that "Regeneration is the repair by growth and differentiation of damage suffered by an organism" and that the processes "are fundamentally of the same nature and follow the same principles as the ontogenetic processes" (Weiss 1939, 458). Some cases involve structural organ or cell repair, other cases bring physiological repair of function. As Donna Haraway has persuasively shown, Weiss turned to the concept of "fields" as a physical way of producing pattern (Haraway 1976, chapter 5). Like Morgan, Weiss concluded that "Here the basic problem of development—how parts which have not been so before become different from one another—rises again in its full important, and if it were for no other reasons, an *epigenetic* view of development would have to be postulated on the strength of regeneration phenomena alone" (Weiss 1939, 478).

Others began to seek chemical explanations for differentiation and development. Early in the last century, Jacques Loeb invoked what he called the "mysterious Fernwirkung." By mid century Joseph Needham summarized a number of such approaches in his 1942 edition of his *Biochemistry and Morphogenesis.* After reminding readers of the variety of studies on regenerating body parts and tissues, he places the discussion in the context of problems of determination, differentiation, cell competence, the power of "organ districts" (areas giving rise to particular organs), renewed cell pluripotency, and questions about abnormal cancers and normal regenerations. He concluded that "Regeneration is a repetition of ontogenesis in so far as the organ districts involved are the same, but the processes of necessity are somewhat different. There is probably a more restricted set of competences in the reacting material, but within the limits of the organ district in question the material is certainly undetermined" (Needham 1942, 447).

About the same time, Jean Brachet took up the question of biochemical effects in his *Chemical Embryology.* Brachet emphasized the formation of blastema, or undifferentiated cells around the edges of the wound. These cells seemed to make possible the development of new cells and differentiation of the right sort to cause regeneration of the original form rather than just new formation of something quite different. Brachet acknowledged that "Whether these cells arise from a migration of adjacent cells or whether they come from a dedifferentiation of more complex cells still is a controversial question" (Brachet 1950, 429).

In 1956, C. H. Waddington took the discussion further. In chapter 14 of his *Principles of Embryology,* he concluded that "The evidence suggests that to some extent at least the formation of a regeneration blastema involves a true dedifferentiation" (Waddington 1956, 306). Yet in other types of regeneration there might be special cells that had never differentiated in the first place. After discussing the role of fields, Waddington attempted to capture the reactions mathematically and asked his readers to focus again, as Child had, on metabolic activity.

Charles Bodemer's 1968 textbook *Modern Embryology* captures the considerable further thinking up to that point. It was clear that regeneration occurs widely, that reconstitution occurs in some cases, that rather little was known about what causes differentiation, redifferentiation, or dedifferentiation, but that these processes were fundamental to understanding developmental biology.

This abbreviated and quite selective review shows that different lines of research considered different aspects of regeneration within the study of development. The path to stem cells and regenerative medicine was neither direct nor clear. Yet there are other stories to tell. For example, WW II stimulated interest in medical reconstructions of lost and injured functions that led to research on regeneration of function through replacement. Sometimes prostheses can do the job, such as with limbs or vision enhancements, but they clearly are not regenerative in any very robust sense. Other medical cases in the 1950s led to discovery of the regenerative capacities of hematopoietic stem cells in bone marrow. These special cells seemed more unique than typical of anything else, and their capacities and limitations surely led many researchers to concentrate exclusively on them and ignore other kinds of cells that did not have the same abilities. It was easy to assume that such stem cells were very rare and special.

Yet another extremely important line of research led to identification, isolation, culturing, and establishing of stem cell lines. This happened in mice, growing out of work at the Jackson Laboratory with the 129 strain of mice that generated teratomas. The regular appearance of these tumors raised the question why, as well as how that mouse strain could help reveal processes of development. Martin Evans and Gail Martin took up the study and by 1981 cultured cell lines from the inner cell mass of mouse blastocysts, thereby generating the first embryonic stem cell lines (Evans and Kaufman 1981; Martin 1981).

This and subsequent successes with mouse cell lines in turn raised questions about whether culturing human embryonic stem cells might also be possible. James Thomson at the University of Wisconsin-Madison finally succeeded in developing non-human primate stem cell lines and then also human stem cell lines cultured

from embryonic stem cells on layers of mouse feeder cells, all in work published in 1998 (for publications and context, see http://ink.primate.wisc.edu/~thomson/publications.html). At the same time, John D. Gearhart at Johns Hopkins used the same basic approach to culture cells from human fetal tissue. Their contributions, as has been well documented, served as a starting point for the push to find ways to culture stem cells for clinical purposes and can be seen as the public starting point for the contemporary Regenerative Medicine movement.

William Haseltine is given credit for the term, including with the short-lived name of a new journal *e-biomed. The Journal of Regenerative Medicine* and in an opening speech at the first regenerative medicine conference in December 2000. The term gained traction, and in 2001, an article in *Nature Biotechnology* noted that the new "`Regenerative medicine' encompasses the broad range of disciplines—and companies—working toward the common goal of the repair or replacement of cells, tissues, and organs." Furthermore, "Regenerative Medicine promises a more permanent solution than current pharmaceutical 'fixes', and with the launch of a few products in this class, it is moving from the realms of science fiction to the surgery" (Petit-Zeman 2001). A search of titles in PubMed shows an increasing number of articles using the term, with a sharp escalation upward in recent years.

12.7 Conclusions: How History and Philosophy of Science Help Make Science Better

We still have a lot more questions than answers about the deep processes of differentiation, dedifferentiation, and regeneration, for example, or of the relations of genetics and development. Yet we know a lot more about the biological processes than we did a century ago. And what we know is very exciting in its prospects for regenerative medicine, though the clinical results will likely be quite different than the public, or even more researchers, now imagine. We are also beginning to recognize the deeper, richer, and older lines of research that have gone into the promising regenerative medicine programs today. We can agree with the eminent cell biologist Edmund Beecher Wilson, who sounded an optimistic note about cell biology in 1896: "We cannot foretell its future triumphs, nor can we repress the hopes that step by step the way may be opened to an understanding of inheritance and development" (Wilson 1896, 330).

What the history and philosophy of science can each do, in large part and in their different but synergistic ways, is to remind researchers of the fact that Wilson pointed to, namely, that of any particular line of research "we cannot foretell its future triumphs." One of the least surprising aspects of good science is that it is often surprising. The breakthroughs often come in different ways and different places then we expected. Historical particulars can show examples of paths not taken, mistaken assumptions that were misleading, failing to ask the important questions that would have stimulated discovery. Philosophical analyses help probe sacred assumptions, articulate questions, and suggest connections unexplored. Taken together, history and philosophy of science help by adding perspective and insight, stimulating the

researcher to challenge assumptions, and to seek different models or methods for exploring the questions at hand.

In the case of regenerative medicine, it has been useful for public purposes and accepted by researchers that translation, stem cells, and regeneration hold tremendous promise for valuable applications. It has been too easy to fall into simplistic pictures of how development works—taking stem cells into culture and transplanting them into the "right" culture medium can seem like a straightforward process. The arrows can seem to point directly from dishes of cells to repaired or replaced structure and function.

We see, in fact, that the research and engineering challenges of regenerative medicine are more complex. Accepting more complex understanding of the science and medical applications will help make the research better. Even if it makes the political sales job harder in the immediate future, honesty should pay off with the public trust in the long run. And history and philosophy of science are useful in getting across the message that success will depend on networks, complex systems of developing organisms and of developing scientific and medical research networks.

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