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ORIGINAL PAPER

Regenerative Medicine in Historical Context

Jane Maienschein

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Abstract The phrase "regenerative medicine" is used so often and for so many different things, with such enthusiasm or worry, and often with a sense that this is something radically new. This paper places studies of regeneration and applications in regenerative medicine into historical perspective. In fact, the first stem cell experiment was carried out in 1907, and many important lines of research have contributed since. This paper explores both what we can learn about the history and what we can learn from the history of regenerative medicine research.

Keywords Stem cells · Regeneration · Regenerative medicine · Ross Granville Harrison · Neuroblast · Thomas Hunt Morgan · Cells · Development · Embryos

"Regenerative Medicine" invokes ideas of generating again and sometimes carries implications of re-birth or revitalization as well as becoming reformed. Yet much of what falls under the label of regenerative medicine has no intention of generating the same form or in some cases even precisely the same function again. Certainly, there is little interest in worrying about generating the same developmental process again, much less the same evolutionary history that got us here. Some of the questions raised include: what is meant by regenerating in each case, what is thought to be doing the regenerating, and how we know. To get at some of the evolving answers to those questions, it is useful to draw on history since today's researchers are informed by earlier work, even when they forget to mention or even notice it.

In particular, the point illustrated here is that many different lines of research fed into and set up the current work in what is called regenerative medicine. When researchers look to the history, they tend to start from where they are today and look back for antecedents. What we find is a number of research lines that are much broader, richer, and older than current focus on translational stem cell research for regenerative medical applications would suggest. For an excellent review of earlier thinking about regeneration, see Alejandro Sanchez-Alvarado's excellent lecture on the American Society for Cell Biology education website [1].

If we look even more widely to the past to discover research programs that looked at some of the same problems, asked some of the same questions, and led to development of some of the same methods and experimental systems, then we find an even richer set of traditions informing research today. It is worth pointing to some of the underlying assumptions, the

J. Maienschein (✉)
Center for Biology and Society, Arizona State University, Tempe, AZ 85287-4501, USA
e-mail: maienschein@asu.edu

roads not taken, the projects taken up and then set aside, and the methods of working and experimental systems adopted—all to gain perspective on the choices made in current regenerative science.

While this short essay cannot pretend to cover the full range of contributions to our current thinking about stem cell research and regenerative medicine, it can point to some lines of research worth further exploration. For example, where did the idea of "stem cells" begin? What were the earliest stem cell experiments? Then, what were some of the major lines of studies of regeneration in the past? And what were some of the central research approaches to fundamental problems of development, on the one hand, or cell and tissue culture on another? These are intended as appetizers to lead readers to other longer and deeper historical explorations, for which my own 2003 book *Whose View of Life: Embryos, Cloning, and Stem Cells* [15] provides one kind of historical introduction, and Hannah Landecker's *Culturing Life. How Cells Became Technologies* provides another. For more discussion of the value of history for science, see the set of essays "What is the Value of History of Science?" in a special section of *Isis* for summer 2007.

Introduction of "Stem Cells": Wilson in 1896

The term "stem cell" was first mentioned in English in 1896, as far as we know, by Edmund Beecher Wilson in his wonderful compendium *The Cell in Development and Heredity*. He followed Theodor Boveri's interpretations of what Boveri saw in *Ascaris* and distinguished those blastomeres that give rise only to differentiated somatic cells and those others, the stem cells, that serve as primordial germ cells and retain a full complement of "large nuclei rich in chromatin" with a different and "peculiar mode of mitosis" [29, p. 111]. Several commentators have pointed out that his meaning was not quite the same as today and was inspired by Valentin Haecker's earlier use of "Stammzelle" to refer to cells that give rise to the germline [23].

Wilson suggested that regeneration might occur as cells that retain a full complement of chromatin become activated by injury. Since Wilson's book remained highly influential on several generations of embryologists, it is worth looking at his interpretation. As Wilson put it:

> Development may thus be conceived as a progressive transformation of the egg-substance primarily incited by the nucleus, first manifested itself by specific changes in the cytoplasm, but sooner or later involving in some measure the nuclear substance itself. This process, which one is tempted to compare to a complicated and progressive form of crystallization, begins with the youngest ovarian egg and proceeds continuously until the cycle of individual life has run its course. Cell-division is an accompaniment, but not a direct cause of differentiation. [29, p. 323]

Researchers did not, Wilson made clear, understand very much about how the processes of differentiation work, but he saw that "the splendid achievements of cell-research in the past 20 years stand as a promise of its possibilities in the future." Finally, "We cannot foretell its future triumphs, nor can we repress the hope that step by step the way may yet be opened to an understanding of inheritance and development" [29, p. 330]. In many ways, we are in much the same situation today, only the "splendid achievements of cell-research in the past 20 years" has taken us astonishingly farther in understanding the roles and capacities of individual cells in development and differentiation.

Stem Cell Experimentation: Harrison and Neuroblasts in 1907

The first stem cell experiment that closely parallels today's stem cell research was Ross Granville Harrison's work on nerve fiber development [8, 9]. If stem cell researchers had paid more attention to history, we could have already had a grand centennial celebration—which is another reason to pay attention to history. This early set of experiments grew out of Harrison's transplantation studies in frogs, where he had been transforming bits of tissue from one frog to another to determine the relative contributions of donor and host. Both Harrison and Spemann learned a great deal about development this way, showing that limb buds or eye vesicles tend to develop in specific ways that are already determined at an early developmental stage.

Harrison's particular interest was in nerve development. As has been well documented, he was

intrigued as many others have been by the question of how complex interactive neural systems arise. It seemed difficult to believe that a bunch of separate cells could just wander around and send out fibers that somehow make up a complex net, yet Harrison was inclined to the view that this sort of epigenetic process is precisely what happens. He entered a discussion about how nerve fibers develop, with a focus on how neuroblast cells extend their fibers out into the surrounding medium as functioning nerve fibers. Harrison hypothesized that these neuroblast cells (neural stem cells in our terms) extend by protoplasmic outgrowth that is directed by the neuroblast and responds to the surrounding medium but is not directed or caused by that medium. Others disagreed, and the evidence up to 1907 had largely depended on silver nitrate preparations led by researchers such as Camillo Golgi and Santiago Ramon y Cajal [2].

Harrison resolved to settle the debate with a crucial experiment. He transplanted neuroblast cells out of the frog altogether and into an artificial culture medium. He used hanging drop methods, a traditional bacteriological technique, to suspend a drop of frog lymph (or other medium) and place a neuroblast cell in it. He predicted that the result would be outgrowth of the nerve fiber, which would look just like what happens in normally developing frog nerve fibers, and from which he therefore inferred that normal development occurs through similar protoplasmic outgrowth from neuroblast cells. The work began while he was at the Johns Hopkins University and continued after he moved to Yale University in 1907. Indeed, under the influence of bacteriologists there, he refined the methods and achieved even greater success [13, 14].

From Harrison's point of view, he had achieved his goal of studying growth and differentiation. Once he had settled this question, he moved on to other embryological questions. He happily set aside tissue culture and left it to others such as Alexis Carrel at the Rockefeller Institute to carry forward. Other methods suited Harrison's questions better, while tissue and cell culture suited more specifically medical interests [11, 12, 24].

Regeneration Research: Morgan in 1901

Meanwhile, however, other biological researchers were focused on regeneration. Among others, Thomas Hunt Morgan stands out for his summary book of 1901 where he sought to bring together all the diverse lines of research on what had been considered regeneration. In his *The Development of the Frog's Egg* [18] just a few years earlier, in 1897, Morgan did not mention regeneration as such but rather pointed to Wilhelm Roux's interpretation of the ability of injured cells to develop even after injury as "postgeneration." Rather than regenerating, the cells began a post-differentiation ability to redifferentiate or postgenerate. Rather than regenerating in the same way as the original differentiation, postgeneration brought a different process for achieving adaptive results. For both Roux and August Weismann, this view of postgeneration involved an activation by injury of extra nuclear determinants.

Morgan did not accept this interpretation himself, which is clear from the text but also from his use of exclamation points indicating his astonishment at Roux's apparently crazy idea: "Roux does not call the embryos that have developed entirely from the material of the non-injured side [in Roux's familiar experiments in which he punctured one of the two first blastomeres with a hot needle to kill it and stop its development], whole embryos of half-size, but he believes that at first there formed a half-gastrula, then a half-embryo. Later this half-embryo completed itself without using material from the injured side! That is to say, by using 'wandering cells' the half-embryo has *postgenerated* the other half of its body!" [19, p. 122]. Yet, even though Morgan found this particular interpretation unacceptable, he spent a number of papers working through why. The problem of how a cell or group of cells can regenerate the whole organism remained a driving question for Morgan, and he saw it as a possible way to get at the causes of morphogenesis.

In 1901, Morgan took a very densely packed 316 pages to describe 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 [25, 26].

One emphasis of all this work was to reject the "dogma" that those parts most likely to sustain injury

have the greatest capacity to regenerate. Morgan demonstrated that this was simply not true, despite the fact that it was a popular argument for adaptability offered by proponents of evolution. In addition, Morgan lamented the tendency of some of his contemporaries to appeal to vitalism to explain the complex phenomena of regeneration while others were "pretending that physics and chemistry will soon make everything clear." Rather to understand the fundamental problems of development of form, "It is possible, I think, by means of experiment alone, to determine how far and in what sense we can pursue the investigation of the causes of form. In this regard experimental studies on the regeneration of animals and plants offer a most admirable field for future work" [20, pp. 206–207].

Regeneration outlined in much more detail the situation as of 1901, both with respect to existing experiments and theoretical interpretations and as to remaining challenges. Morgan came to see regeneration as a special problem, providing ways 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 has analyzed "Morgan's ambivalence" reflected in Morgan's tensions hypothesis for regeneration. Wolpert notes that at times Morgan's interpretation seems very like the gradient theory of Charles Manning Child, and that Wolpert himself favors and has developed so vigorously since. At times, Morgan seemed to embrace gradients and rely on them to explain polarity and other phenomena. Yet at other times, Morgan turned away from such proposed gradients and reverted to alternative accounts. And, 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 [17, 31]. At that time, neither gradients nor tensions really advanced understanding of regeneration, since neither Morgan nor Child got far in showing how either gradients or tensions actually work nor what causes them. Saying that gradients cause regeneration but that we have no idea how gradients are established in the first place does not get us very far, as Morgan explained.

Induction and Cloning

The 1920s also brought interest in the phenomena of "induction" and the role of what Hans Spemann identified as the "organizer." Could it be that chemical forces and factors caused induction (in which some tissue or cells seemed to carry the cause that stimulated the process of 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. Instead, really focusing on inductive processes in large eggs of frogs seemed more productive for those such as Harrison, Spemann, and their many students [6].

One line of research involved continuing to transplant all sorts of parts: limb buds and eye vesicles still, but also bits of "organizer" material from the dorsal lip of the frog blastopore. Or other random materials to see whether they could induce differentiation and how. Still others transplanted nuclei into egg cells, leading to Robert Briggs and Thomas King's successful cloning of the frog's egg in 1951 and John Gurdon's demonstration that even later developmental stages in frogs could donate nuclei and produce cloned adults. 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.

Experimental Embryology

Meanwhile, by 1934, after spending decades studying genetics in fruitflies and winning a Nobel Prize for the work of his laboratory group, Morgan returned to regeneration as a foundational problem in embryology. It became clear that he had never really given up his fascination with regeneration as a puzzling phenomenon. In *Embryology and Genetics* in 1934, he noted that it had become apparent that 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" [21, p. 164].

Here we see Morgan's great ability to articulate a foundational question with clarity:

> This brings up once more the question of the role of genes in these regenerative changes. Since all cells contain a full complement of genes it would seem that every cell is capable of forming part of the organism, except in so far as its protoplasm has already been irreversibly changed in a given direction. On this supposition it would seem more likely that the old cells would then continue to function in the new part as before, and, in fact, this is obviously true in many cases, but in the cells that change over into different tissues this explanation will not apply. Perhaps all that can then be said is that after losing contact with their original tissues certain cells may lose their differentiation (and observation substantiates this) and then begin to develop according to their location. [21, p. 169]

Morgan was well aware that "location" may be everything, but that invoking it explains nothing. Perhaps the new cells' contact with cells at the edge of the area being regenerated exert some chemical influence, and the old cells act as sort of "determiners or organizers" for the new cells. He noted quite presciently that "This kind of evidence does not help to decide whether the genes are all acting while these differentiations in the cells are taking place, or whether certain sets are brought into action by the new environment of the cells of the new part" [21, p. 169].

For Morgan, regeneration was a fundamental problem of development and differentiation, and it was primarily a problem of form. This remained true for most other embryologists, who largely focused more on morphogenesis than on physiology and problems of function. In 1927 and 1931, for example, Eugen Korschelt published a magnificent two volume study of *Regeneration und Transplantation*. He started with the premise that "Regeneration is the ability of organisms to replace parts of the body which have been lost" [10, p. 1]. For Korschelt, transplantation experiments involved such cases of loss and replacement of form and afforded excellent examples to study in detail the resulting processes of development. This large work provides a valuable summary of experimental work to date, drawing together traditional studies of regeneration of parts with those of experiments in transplantation.

Theories of Cells and Development

Others took a more theoretical approach. Paul Weiss, for example, asserted in his 1939 *Principles of Development* that "Regeneration is true development." That is, "Regeneration is the repair by growth and differentiation of damage suffered by an organism past the phase of primordial development." The processes, he insisted, "are fundamentally of the same nature and follow the same principles as the ontogenetic processes" [28, p. 458]. Some cases involve organ or cell repair, other cases bring physiological repair of function. As Donna Haraway has discussed very persuasively, Weiss turned to the concept of "fields" as a physical way of producing pattern [7, Chap. 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 import, 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" [28, p. 478].

Others began to seek explanations for the fields or gradients or tensions or induction or whatever it was that caused such epigenetic development in chemistry. Jacques Loeb, for example, explored chemical explanations starting at the beginning of the twentieth century, including with his idea of what he called the "mysterious Fernwirkung." By mid century, Joseph Needham summarized a number of such approaches when reviewed the range of regenerative phenomena in his 1942 edition of his *Biochemistry and Morphogenesis*. After reminding his readers of the variety of studies on regenerating body parts and tissues, he placed 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 pluritpotency and questions about abnormal cancers and normal regenerations. In a section on "Biochemical aspects of

regeneration," he concluded with a summary and with more questions: "Regeneration is a repetition of ontogenesis in so far as the organ districts involved are the same, but the processes of necessity 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" [22, p. 447].

About the same time, Jean Brachet took up the questions of biochemical effects in a chapter on "Biochemistry of the Organism during Regeneration" in his *Chemical Embryology*. This volume appeared first in French in 1944 with the first English translation in 1950. Brachet emphasized the phenomenon that others had begun to regard as particularly important, namely the formation of blastema, or undifferentiated cells that gathered around the edges of a wound. These cells seemed to make possible the development of new cells and differentiation of the right sort cause regeneration of the original form rather than just new formation of something quite different. Brachet noted 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" [4, p. 429].

In 1956, C.H. Waddington took the discussion further, drawing on multiple lines of research to that point. Chapter Fourteen of his *Principles of Embryology* considered "Regeneration" and the multiple ways regenerative processes can occur. His focus on "regeneration cells and their potentialities" worked to get at just how those clusters of cells capable of regenerating lost parts work. He concluded that "The evidence suggests that to some extent at least the formation of a regeneration blastema involves a true dedifferentiation" [27, p. 306]. Yet in other types of regeneration it was less clear whether there were special cells that had never been differentiated in the first place. After discussing the role of fields, Waddington offered mathematical equations to attempt to capture the reactions and asked his readers to focus again, as Child had, on the level of metabolic activity in regeneration as in embryology generally.

By 1968, Charles Bodemer summarized these various approaches and conclusions in his introductory textbook in *Modern Embryology*. He explicitly followed in the path of Lester G. Barth and offered a full chapter on regeneration. Bodemer noted that normal development and regeneration are very similar but not identical. He also pointed to the importance of the cellular aggregation called the blastema [3, pp. 336–339] as the source of material for regeneration. Some organisms like planarians have a reservoir of undifferentiated cells and what seem to be completely omnipotent cells, called neoblasts, while other organisms seem to rely more on dedifferentiation of cells such as occurs in amphibian limb regeneration. Bodemer raised the possibility that "the ability of organisms to regenerate is not lost as such, but in addition to changes in such systemic factors as hormones, there may be conditions of healing and innervation that create a block to the dedifferentiation, proliferation, and growth of cells. If this block is overcome, regeneration may be expected in those forms that do not normally regenerate" [3, p. 348].

Bodemer's text also reflected a growing conviction that "reconstitution" was possible, as Henry van Peters Wilson had shown in 1907 when he disaggregated sponge cells and they reconstituted sponges [30]. By the 1960s, it was clear that regeneration occurs widely, that reconstitution occurs in some cases, that we knew rather little about what causes differentiation or redifferentiation or dedifferentiation, but that these processes were fundamental.

Regenerating Function

What this abbreviated and rather idiosyncratic review shows is that there were several different lines of research concerned with different aspects of regenerative phenomena. The path to stem cells and regenerative medicine was neither direct nor clear. So far, I have focused mainly on studies of morphogenesis. That is because the embryologists were largely morphologists at heart until at least the 1960s. They largely held that function would follow form. The possibilities for regenerating or replacing function without replacing the same form were not really seriously considered by embryologists, who were the ones most focused on regeneration into the 1960s.

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.

Meanwhile, other kinds of medical cases led to discovery of the regenerative capacities of hematopoietic stem cells in the 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 to ignore others kinds of cells that did not have the same abilities. It was easy to assume that such stem cells were rare and of very restricted kinds.

Mouse Cell Lines

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 research on pluripotent stem cells, which were named by Leroy Stevens based on his 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 managed to culture cell lines from the inner cell mass of the mouse blastocysts, thereby generating the first embryonic stem cell lines [5, 16].

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

Conclusion

As embryology, with its focus on embryonic emergence of form, gave way to the field of developmental biology, research shifted to molecular genetics and deemphasized cells and traditional foundational questions of morphogenesis, generation, and regeneration. Yet studies of regeneration continued through different kinds of questions, different methods, and carried out by a diversity of researchers drawing on different backgrounds and with diverse goals. Elements of these different lines of research have begun to converge in new ways in what is called regenerative medicine.

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 most researchers, now imagine. We also are beginning to recognize the deeper, richer, and older lines of research that have gone into the promising regenerative medicine programs today. To return to Wilson's optimistic note in 1896 concerning cell theory, about regenerative medical research: "We cannot foretell its future triumphs, nor can we repress the hopes that step by step the way may yet be opened to an understanding of inheritance and development" [29, p. 330]. Yes, indeed. And we gain perspective, and humility, by keeping in mind the deep, broad, and rich diversity of historical lines leading to today's efforts in regenerative medicine.

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Author Biography

Jane Maienschein is Regents' Professor, President's Professor, and Parents Association Professor at Arizona State University, where she directs the Center for Biology and Society. She has served as president of the International Society for History, Philosophy, and Social Studies of Biology and the History of Science Society; served as science advisor to her Congressman, and has won awards for her teaching and public engagement. Among her dozen (co)edited and authored books is *Whose View of Life? Embryos, Cloning, and Stem Cells* with Harvard University Press.