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Rediscovering the Immortal

Hydra: Stem Cells and the Question of Epigenesis

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If there were no regeneration, there could be no life. If everything regenerated there would be no death.

—R. J. Goss, *Principles of Regeneration* (1969)

The authors of a recent textbook attribute the original impetus to experiment with human stem cells to the observation of extraordinary regenerative powers in certain animals:

Early evidence that stem cells exist in the somatic tissues of animals arose from observations of the regeneration of entire organisms, including the head, from small sections of the *Hydra* soma. Substantial somatic regeneration also occurs among other invertebrates, including members of relatively highly organized groups such as annelids. Limb regeneration can also be observed in insects and, among vertebrates, this property extends to the amphibians, which can regenerate the distal portions of limbs following their amputation.¹

1. David R. Marshak, David Gottlieb, and Richard L. Gardner, "Introduction: Stem Cell Biology," in *Stem Cell Biology*, ed. idem (New York: Cold Spring Harbor Laboratory Press, 2001), p. 10. In a recent article, Jane Maienschein establishes a similar genealogy of conceptual associations at the basis of contemporary stem cell research: "How is it that some organisms, some of the time, and for only some cells, are capable of regenerating injured parts? Crabs can regenerate a claw, but humans cannot regenerate a hand. Worms can regenerate most of their segmented bodies, and snakes regularly regenerate their skins. Why, how, when, under what conditions, and can we use an understanding of such processes to develop medically useful applications, researchers asked" (Jane Maienschein, "What's in a Name: Embryos, Clones, and Stem Cells," *American Journal of Bioethics* 2:1 [2002]: 12–19, on p. 10).

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The concept of regeneration refers to the ability of the developed organism to replace lost tissues or organs through the growth or remodeling of somatic cells. As the authors of this introduction observe, some animals possess remarkable powers of self-regeneration. Flatworms and starfish can regenerate whole organisms from isolated fragments. Chop a flatworm (planarian) into a hundred pieces, feed it occasionally, and it will grow back as a hundred perfectly formed new worms. Insects can grow new legs. Among vertebrates, newts and other amphibians are capable of restoring limbs, tails, lower jaws, and even the eye lens. Perhaps most astonishing of all, the tentacle-waving freshwater coelenterate *Hydra* is not only able to survive amputations, it can also be dissolved into a single-cell solution, from which it will reconstitute itself over a period of weeks.

Humans and other mammals seem to be precluded from these extreme feats of self-regeneration, although the textbook authors point out that the formation of multiple tissues during wound healing is consistent with the possibility that mammals “have retained progenitor [stem] cells capable of repairing limited damage to organs.”² They also observe that certain tissues of the adult human body retain a limited potential for self-renewal throughout life: Skin is constantly shed and renewed. The entire adult human skeleton is regenerated every eight to ten years. Blood cells, gut epithelium, epidermis, and the cellular lining of the uterus are all replaced on a regular basis, while liver, muscle, and blood vessels have a more restricted capacity for self-repair. These processes have been attributed to resident *adult stem cells*—cells that are able to turn into and replace specific differentiated cell types, as they age and die, while at the same time continuing to renew themselves in an undifferentiated state.

The authors go on to note that the cellular dynamics involved in adult mammalian tissue repair are highly “reminiscent” of those occurring in early embryological development. Not only does wound healing, in its own limited way, recall the more plastic self-regenerative capabilities of the newt, the flatworm, and the *Hydra*, but it also seems to partially reenact the processes of embryogenesis. This observation points to a further chain of associations, one that has contributed to the experimental isolation of *embryonic stem cells* (ES cells)—cells that, when isolated from the inner cell mass of the early embryo, are able to renew themselves indefinitely in an undifferentiated state while also giving rise to many if not all of the differentiated cell types of the body.

What interests me here is the conceptual movement that leads the writers of this introduction from the spectacular self-regenerative

2. Marshak, Gottlieb, and Gardner, “Introduction” (above, n. 1), p. 10.

acts of *Hydra*, amphibians, and flatworms, to the dynamics of tissue renewal in the adult human body, and back again to the process of mammalian embryogenesis. In what sense does this line of inquiry inform the technical ambitions of stem cell research? If such diverse phenomena can be attributed to the different actualizations of the “stem cell,” as the authors seem to claim, might it be possible to treat them as more or less extreme cases of one fundamental process of morphogenetic (re)generation? More pointedly, might it be possible to provoke the extreme restorative powers of self-regenerating animals in the tissues of adult humans, or to enhance the limited wound-healing powers available to adult bodies with the regenerative capacities of early embryos?³ It is these questions, I would suggest, that animate the experiments currently being pursued in the field of regenerative medicine.

These questions are not entirely new. With their insistence on the relation between stem cells, developmental processes, and the phenomena of regeneration, contemporary theorists, perhaps unwittingly, are revisiting a problematic that has been at the center of debates between epigenetic and preformationist theories of biological generation since the late seventeenth century. Scientists in the modern epigenetic tradition have consistently looked to the same bestiary of self-regenerating *Hydra*, newt limbs, and worm segments in their efforts to theorize the processes of biological self-organization, while preformationists have encountered self-regeneration as an intractable problem.

3. This question is explicitly addressed in the following recent works: David L. Stocum, *Wound Repair, Regeneration and Artificial Tissues* (Heidelberg: Springer-Verlag, 1995); idem, “Bridging the Gap: Restoration of Structure and Function in Humans,” in *Cellular and Molecular Basis of Regeneration: From Invertebrates to Humans*, ed. Patrizia Feretti and Jacqueline Géraudie (New York: Wiley, 1998); Arnold I. Caplan, “*In Vivo* Remodelling,” in *Reparative Medicine: Growing Tissues and Organs*, ed. Jean D. Sipe, Christine A. Kelley, and Loré Anne McNicol, *Annals of the New York Academy of Sciences*, vol. 961 (New York: New York Academy of Sciences, 2002), pp. 307–308. Stocum, for example, looks to the example of epimorphic regeneration in amphibia and argues that “if epimorphic regeneration is an ancestral property that has been polyphyletically suppressed in favour of wound healing and tissue regeneration,” this could mean that “animals such as ourselves may have retained the potential for epimorphic regeneration, and if the mechanism of such regeneration can be understood in organisms like salamanders, this potential might be actualized” (*Wound Repair*, p. 5). Caplan makes a similar claim in relation to embryogenesis, arguing that a “fundamental principle of reparative medicine which governs our efforts to regenerate differentiated tissue is to organize the reparative circumstances to *recapitulate selected aspects of embryonic developmental sequence*, including attempts to mimic the embryonic microenvironment in which tissue initiation, formation, and expansion take place” (“*In Vivo* Remodelling,” p. 307). For a more general overview of recent work relating stem cells to the question of regeneration, see Helen Pearson, “The Regeneration Gap,” *Nature* 414 (2001): 388–390.

In this article, then, I want to resituate the recent history of stem cell research within a longer tradition of experimental studies in regeneration, and within the speculative horizon defined by epigenetic theories of self-organization. At the same time, I want to suggest that the technological intervention that has led to the isolation of stem cells has also fundamentally challenged the limits within which the principle of self-organization can be thought. At issue here is the relationship between cellular “potency,” differentiation, and “form” in processes of regeneration. In this respect, I will suggest that there is more than an incidental relation between the models of self-regenerative growth traditionally cited in epigenetic studies and the contemporary developments of regenerative medicine. Stem cell research returns to some of the abiding enigmas of the epigenetic tradition, and in the process it rediscovers the strange properties of one of its privileged experimental models—the immortal freshwater polyp *Hydra*.

Discovering the *Hydra*

When, in the seventeenth century, the English anatomist William Harvey resumed the embryological studies of Aristotle, he reiterated the principle that development in the higher animals should be regarded as epigenesis—the creative, incremental self-organization of form out of unstructured matter.

The founders of microscopic anatomy, on the other hand, argued that all developed form preexists in the germ, one generation encapsulated in the other from the beginning of time, although there was debate as to whether the germ was to be located in the ovum or sperm. Preformationists tended to view the actual process of development as inevitable, mechanistic, and irrelevant, since its unfolding was assumed to be wholly determined, as if by clockwork, before it actually occurred. When the microscopists saw minute zoa swimming in drops of semen, they thought they were looking at homunculi, miniature humans that only needed to be unwrapped into being.⁴

4. I am unable to do justice here to the complex chronology of debates between preformationism and epigenesis. For a thorough discussion of the legacy of Aristotelian natural philosophy in the epigenetic tradition, as well as a general history of the debate between preformationism, the theory of preexistence, and epigenesis, see Jacques Roger, *The Life Sciences in Eighteenth-Century French Thought*, trans. Robert Ellrich (Stanford, Calif.: Stanford University Press, 1997). See also Elizabeth B. Gasking, *Investigations into Generation 1651–1828* (London: Hutchinson, 1967); Helmut Müller-Sievers, *Self-Generation: Biology, Philosophy, and Literature around 1800* (Stanford: Stanford University Press, 1997). I have also investigated the implications of contemporary stem cell research from the point of view of Aristotle’s epigenetic philosophy, in Melinda Cooper, “The Living and the Dead: Variations on *De Anima*,” *Angelaki: Journal of the Theoretical Humanities* 7:1 (2002): 81–104.

The doctrine of preformation encountered several immediate and enduring problems—enigmas of animal generation that refused to be explained within the prevailing categories of encapsulated ova or sperm. These enigmas included the simple phenomena of hereditary resemblance and hybridization, as well as monstrous births or “teratisms”; but of more immediate interest, for the purposes of my argument, was the problem of regeneration.⁵ If development is wholly predetermined in the egg or sperm, how is it possible for the body to continue to regenerate itself in response to the contingencies of loss? Throughout the first half of the eighteenth century, successive discoveries and experiments in animal regeneration posed a persistent challenge to the then dominant theory of preformation.

In 1712, the French preformationist René-Antoine Ferchault de Réaumur presented a report before the *Académie royale des sciences de Paris* in which he recounted the regeneration of crab, lobster, and crayfish claws and commented on an earlier report on self-regenerating lizard tails made by Melchisédech de Thévenot in 1686. Réaumur’s efforts to grapple with the philosophical problems associated with self-regeneration inspired his young Genevan correspondents, Abraham Trembley and Charles Bonnet, to pursue his experiments. In 1740, Trembley made a chance discovery that would have a decisive, though delayed, effect on the future course of natural philosophy: having collected jars of water from freshwater ponds, he discovered a small, tentacled creature (later christened the *Hydra* polyp by Réaumur) that appeared to possess the characteristics of both plants and animals.⁶ At first glance, the *Hydra* looked like a water plant—but, unlike a plant, it contracted when touched, was able to move along glass like an inchworm, and seemed to wave its tentacles of its own accord when catching food. These green plant-like creatures seemed to be endowed with Aristotle’s sensitive soul, characteristic of animals. In an effort to resolve the question once and for all, Trembley cut the creature into little pieces, expecting that an animal would never survive its dissection. But although he was by now

5. For a detailed discussion of these three points of resistance to the theory of preexistence, see Roger, *Life Sciences* (above, n.4), pp. 308–353.

6. Primary sources and translations relating to the discovery of the *Hydra*, and detailed discussions of its significance for the theory of generation, can be found in Virginia P. Dawson, *Nature’s Enigma: The Problem of the Polyp in the Letters of Bonnet, Trembley, and Réaumur* (Philadelphia: American Philosophical Society, 1987); Sylvia G. Lenhoff and Howard M. Lenhoff, *Hydra: The Birth of Experimental Biology—1744: Abraham Trembley’s Mémoires concerning the Polyyps* (Pacific Grove, Calif.: Boxwood Press, 1986). See also Roger, *Life Sciences* (above, n. 4), pp. 312–318, for a discussion of the role of regeneration studies in questioning the premises of preformationism.

convinced that the *Hydra* was indeed an animal, its amputated fragments proceeded to grow back as so many new little *Hydra*, just like the cuttings of a plant. The more he chopped up his *Hydra*, the more *Hydra* regenerated. In a letter to Bonnet dated December 22, 1741, he recounts these dissection experiments in detail:

I made *Hydras* with seven and eight heads, by cutting them lengthwise part way down the body beginning at the head. Then I did the exploit of Hercules. I valorously cut off the seven heads from one *Hydra*. Seven heads came back, and what is more, each of the seven heads which were cut off will soon be in a state to become a *Hydra*. For this I am careful to nourish them well. I have a polyp which was already cut in 36 parts and most of these 36 multiply and would multiply if I wished it.⁷

The same year, Trembley also discovered that *Hydra* are able to reproduce asexually through a process that he likened to budding in plants, the offspring emerging progressively from the body of the parent like the offshoot of a branch. The possibility of asexual reproduction in animals was not new to Trembley: earlier experiments carried out by his friend Bonnet had confirmed that aphids are able to reproduce through parthenogenesis. But the asexual reproduction of the *Hydra* had more-unsettling implications—its mode of reproduction appeared as a simple variation on its self-regenerative properties. The division between generations was here seriously in question.

The publication of Trembley's monograph in 1744 led to a series of further discoveries in the field of regeneration. The following year, Bonnet reported regeneration in freshwater worms, and much later he studied the regeneration of the newt's eye. Lazaro Spallanzani, in his 1768 *Prospectus*, detailed experiments on the regeneration of legs and tails in newts and tadpoles and reported the spontaneous regrowth of heads in decapitated snails. Later studies recorded regeneration in planarians (or flatworms), aquatic worms, starfish, and certain earthworms.⁸ It was Trembley's *Hydra*, however, that continued to provoke the most far-reaching interrogations of the preformationist tradition and its philosophical premises. These interrogations would be obsessively rehearsed by Charles Bonnet, as he struggled to reconcile the doctrine of preformed germ and unitary soul with the discon-

7. Translated and quoted in Dawson, *Nature's Enigma* (above, n. 6), p. 164; the original French version is transcribed on p. 207.

8. For a historical overview of studies in regeneration from the late seventeenth century through to the twentieth, see the articles in Charles E. Dinsmore, ed., *A History of Regeneration Research: Milestones in the Evolution of a Science* (Cambridge: Cambridge University Press, 1991).

certing proliferative feats of the *Hydra*. If the body is divisible and regenerable, he asked, must we assume that the soul is also endlessly divisible, and thus capable of regenerating form from the minutest, basest body part, even the tail of a worm? Should we assume that the body contains preexistent germs for each tentacle, tail, or limb?

Like Réamur, Bonnet ended up using the problem of regeneration as a critical pretext for consolidating the doctrine of preformationism. He ultimately resolved the enigma of self-regenerative animals by compensating, as it were, for the shortcomings of a unitary, determinist theory of generation: if the *Hydra* and other animals are able to restore body parts, he argued, it is because multiple germs with soul-like properties are distributed throughout the body, ready to unfold when needed.

Canonizing the *Hydra*

This discovery of the *Hydra* was to be canonized in Immanuel Kant's definitive formulation of the epigenetic principle of self-organization, through the intermediary of the German natural scientist Johann Friedrich Blumenbach. In 1781, Blumenbach published a treatise entitled *Über den Bildungstrieb und das Zeugungsgeschäfte* (The formative drive and its relation to the business of procreation), in which he reproduced earlier experimental studies on freshwater *Hydra* and established a connection between their regenerative powers and the processes of healing and scarring in humans. In a theoretical statement that was to establish the dominance of the epigenetic model within the life sciences, Blumenbach surmised that development must be understood as the encounter between a receptive, unformed matter and a formative drive that remains continuously at work within the body:

in the previously unformed generative matter of the organized body, after it attained its maturation and arrived at the place of its destiny [namely the womb], a particular, lifelong active drive is stirred up to initially shape its definite form, then to preserve it for a lifetime, and if it by chance becomes mutilated, to reestablish it if possible.⁹

In order to distinguish this particular drive from the other kinds of vital force at work in the body (contractility, irritability, sensibility), Blumenbach defined it as the formative drive (*nisus formativus*).

It is with implicit reference to this work that Kant distinguishes the modes of causality proper to organisms and to machines in his

9. Johann Friedrich Blumenbach, *Über den Bildungstrieb*, quoted and translated in Müller-Sievers, *Self-Generation* (above, n. 4), p. 43.

Critique of Judgement.¹⁰ Kant here defines an organism as a being for whom the parts are reciprocally cause and effect of the whole. The purposiveness of the organism represents an internal self-formative force, allowing the organism both to preserve its form and to reproduce itself as genus. A tree, for example, is able to generate another tree, therefore (re)producing itself as species: "Hence with regard to its *species* the tree produces itself, it is both cause and effect, both generating itself and being generated by itself ceaselessly, thus preserving itself as a species."¹¹ The tree also constantly regenerates itself in its individual form through the process of nutrition and growth.¹² Finally, Kant points to the example of tree grafting to argue that the tree is capable of purposive self-regeneration even from its separate parts:

part of the tree also produces itself inasmuch as there is a mutual dependence between the preservation of one part and that of the others. If an eye is taken from the leaf of one tree and set into the branch of another, it produces in the alien stock a plant of its own species, and so does a scion grafted onto the trunk of another tree. Hence even in one and the same tree we may regard each branch or leaf as merely set into or grafted onto it, and hence as an independent tree that only attaches itself to another one and nourishes itself parasitically.¹³

This final example leads Kant to the favorite epigenetic example of spontaneous tissue regeneration, which, in his words, represents one of the "most marvelous properties of organized creatures," for "if such beings are injured, nature aids itself, and the loss of a part that was needed to sustain [*erhalten*] adjoining ones is made up by the rest."¹⁴

In short, according to the example of the tree, the organism can be defined as self-regulative, self-regenerative, and above all self-(re)productive within the limits of a purposive whole. It is in this triple sense that Kant understands the principle of self-organization in nature:

10. For a detailed discussion of the relation between Kant and Blumenbach and the importance of epigenetic theories in general in Kant's *Critique of Judgement*, see Müller-Sievers, *Self-Generation*, pp. 41–64. See also Timothy Lenoir, "Kant, Blumenbach, and Vital Materialism in German Biology," *Isis* 71 (1981): 77–108. I am indebted to Müller-Sievers's study for alerting me to the resonances between Kant's philosophy of self-organization and Blumenbach's studies on the *Hydra*.

11. Immanuel Kant, *Critique of Judgement*, trans. Werner S. Pluhar (Indianapolis: Hackett, 1987), § 64, p. 249.

12. *Ibid.*, § 64, p. 250.

13. *Ibid.*

14. *Ibid.*

In such a product of nature, just as each part exists only *as a result* of all the rest, so we also think of each part as existing *for the sake* of the others and of the whole, i.e., as an instrument (organ). But that is not enough. . . . Rather, we must think of each part as an organ that *produces* the other parts (so that each reciprocally produces the other). . . . Only if a product meets that condition [as well], and only because of this, will it be both an *organized* and a *self-organizing* being, which therefore can be called a *natural purpose*.¹⁵

The machine, on the other hand, possesses no self-organizing power—its cause lies outside itself in the motive power (*bewegende Kraft*) of its creator, a power that can be likened to the external generative principle assumed by the preformationists. Implicitly, then, Kant's model of the organism argues that preformationist theories can explain only the fabrication of machines and offer no insight into the epigenetic forces peculiar to organic life:

Hence an organized being is not a mere machine. For a machine has only *motive* force. But an organized being has within it *formative* force, and a formative force that this being imparts to the kinds of matter that lack it (thereby organizing them). This force is thereby a formative force that propagates itself—a force that a mere ability [of one thing] to move [another] (i.e., mechanism) cannot explain.¹⁶

In 1790, then, Blumenbach's *nisus formativus* was formalized in the Kantian principle of organic self-organization—a principle that has always informed the epigenetic perspective on (re)generation and has recently undergone something of a revival under the joint influence of cybernetics and complexity theory.¹⁷ In their more recent guise however, theories of self-organization seem to be pushing beyond the limits of Kant's original conception. For Kant, after all, natural purposiveness is confined within the limits of a form or a whole: in his words, the parts of a body “must through their own causality, produce one another as regards both their form and combination, and . . . in this way . . . produce a whole.”¹⁸ And even when he cites the extreme cases of tree grafting and limb regeneration, it would seem, Kant in no way interrogates the interdependency of

15. *Ibid.*, § 65, p. 253.

16. *Ibid.*, § 65, p. 253.

17. For an early overview of current work on biological self-organization, see P. Dumouchel and J. P. Dupuy, eds., *L'auto-organisation (Colloque de Cérisy)* (Paris: Seuil, 1983). For a more recent historical overview, see Evelyn Fox Keller, *The Century of the Gene* (Cambridge, Mass.: Harvard University Press, 2000), pp. 106–111, who traces the persistence of theories of self-regulation throughout the twentieth century.

18. Kant, *Critique of Judgement* (above, n. 11), § 65, p. 252.

self-production and totalization within the purposive whole of the organism. How then, we might ask, did he account for Blumenbach's *Hydra*, which seem to possess a power of proliferative, cumulative self-regeneration not easily containable within the principle of form? The most extreme implications of this early experimental model are perhaps only now being explored.

Weismann

It is indicative of the subsequent fortunes of epigenesis in twentieth-century biological theory that August Weismann, who would exert a lasting influence on both evolutionism and genetics, formulated his theory of germinal heredity against the principle of self-organization.

Writing in the last decades of the nineteenth century, Weismann, on his own admission, was motivated by the desire to definitively sever Darwinian evolution from the Lamarckian thesis of acquired characteristics. Darwin's theory of pangenesis clung to aspects of Lamarckian evolution. Weismann, on the other hand, wanted to establish natural selection as the sole driving force of evolution by supplementing it with a rigorous theory of heredity, based on the fundamental distinction between the inheritable germ line and the perishable soma or body. At the same time, he sought to purge Darwin's work of all residual traces of the epigenetic current and its traditional problematic of growth, nutrition, and development. In the preface to the English translation of his major work, *The Germ-Plasm: A Theory of Heredity*, Weismann recounts that he had at first been tempted by the concerns of the epigenetic tradition, but ended up convinced that only the theory of evolution (preformation) was compatible with natural selection.¹⁹ What he offered was a theory of transmission, rather than insight into the processes of vital organization—since the latter, he claimed, were in any case predetermined by “vital morphological units” or biophores contained in the nucleus of cells. For Weismann, life itself resides in the germinal substance, which transcends and predetermines the properly epigenetic processes of development, and is transmitted from generation to generation.

Drawing on contemporary experiments in cell theory showing that the reproductive cells divide differently from the other cells of the body, Weismann surmised that, in most multicellular animals, one of the earliest cell divisions would give rise to all the somatic cell lines in their difference from the immortal germ cell line (egg or

19. August Weismann, *The Germ-Plasm: A Theory of Heredity* (London: Walter Scott, 1893), pp. xiii–xiv.

sperm). This primordial moment of scission would establish an irreversible division of labor between the germ cells, which at fertilization unite to exchange the inheritable genetic legacy of the parents, and the somatic cells, which merely develop or materialize the structures dictated by the germ line. From this point on, the germ line, as the immortal substance of heredity, would be sequestered from the soma. Transmissible from generation to generation through the intermingling of egg and sperm, the germ cells would be immune to any variation of the somatic cells in the course of development. Inheritable variation, when it occurred, could be attributed only to chance mutations in the germ cell line.

While he rigorously distinguished the generative power of the germ plasm from the passive soma, Weismann also surmised that the germ plasm is distributed in the nuclei of the somatic cells through successive cellular divisions, so that each contains a different fragment (or ideoplasm) whose “determinants” dictate its specific character. The differentiation and organization of cells, Weismann argued, is strictly predetermined from within, on a singular basis, precluding any mutual, formative interaction *between* cells.²⁰ He was insistent on this point, despite experiments carried out on sea urchin blastomeres by the contemporary epigenetist Hans Driesch, indicating that the “relative position of a blastomere in the whole determines in general what develops from it; if its position be changed, it gives rise to something different. In other words its prospective value is a function of its position.”²¹ For Weismann, it was a fundamental theoretical premise that somatic life could be endowed with no immanent power of self-organization. On this point, as he explains himself, the theory of heredity reattributes the reciprocal causality of Blumenbach’s *nisus formativus* to the one-way determinism of the germ plasm, redistributing its generative powers in particle form to the ideoplasm of each cell:

The “*nisus formativus*” descends from its previous position as a single force directing the whole, and breaks up into an unlimited number of material particles which are situated in the individual cells, and each of which prescribes the course of life of the cell. These particles are determined as regards their kind, and are distributed to their proper places.²²

20. *Ibid.*, pp. 106, 134–136.

21. Quoted in Jan Sapp, “Concepts of Organization: The Leverage of Ciliate Protozoa,” in *Developmental Biology: A Comprehensive Synthesis*, vol. 7 of *A Conceptual History of Modern Embryology*, ed. Scott F. Gilbert (New York/London: Plenum Press, 1991), pp. 229–258, on p. 236.

22. Weismann, *Germ-Plasm* (above, n. 19), p. 105.

It is not surprising, then, that Weismann, like his preformationist predecessors, would encounter the problem of regeneration in the mode of an enigma, to be reassimilated back into the categories of germ line and soma at any cost. Weismann's question is essentially the same one that troubled Bonnet: If determination is irreversible and occurs once and for all, how can it be suspended, reversed, and reactivated in response to developmental contingencies—as it appears to be when plants proliferate from a cutting, when animals regrow lost limbs or sprout new buds, or even when the cells of some human tissues are shed and renewed? In part 2 of *The Germ-Plasm*, Weismann dedicates a whole chapter to the consideration of the various phenomena of regeneration—including the regeneration of whole plants from somatic cells, of amphibian and reptile limbs, and, of course, the extreme example of the *Hydra*—in an effort to respond to some of the critiques that had already been formulated by botanists and embryologists in the epigenetic tradition. He is quite open about the difficulty of accommodating phenomena of regeneration within his determinist theory of transmission:

It does not follow directly from what has already been said with regards to the structure of the germ-plasm, that lost parts can be more or less completely replaced. The only deduction that can be made so far is that all the parts of which the organism is composed are formed *once* during the development of the organism from the egg: no explanation is given of the fact that individual parts can be produced a *second time*, when they have been lost by the action of external circumstances. . . . We must now therefore attempt to explain the fact that a part of the body can nevertheless be reconstructed.²³

Weismann precludes the possibility that the cells of the organism might be available to collective, emergent processes capable of responding to fluctuations in their epigenetic field. Regeneration, he insists, is not a fundamental defining property of life.²⁴ If certain organisms are nevertheless capable of regeneration, it is because some of their cells have been *determined more than once*, and thus contain both operative and latent determinants, the latter becoming active in response to loss or injury.²⁵ Worms that can regenerate the head and the tail must possess cells containing two supplementary determinants; the *Hydra*, which can regenerate in three different directions, must contain three.²⁶

23. *Ibid.*, p. 93.

24. *Ibid.*, pp. 105, 114.

25. *Ibid.*, p. 109.

26. *Ibid.*, pp. 126, 127.

But for Weismann, the problem of regeneration proves even more intractable than it had been for the preformationists of the eighteenth century, since it also calls into question his theory of evolution. How does his interpretation of Darwin, which designates the germ line as the exclusive target of natural selection, account for the evolution of life forms that regenerate, grow, and “evolve” in the absence of a strict division between germinal substance and soma? As Weismann himself points out, a distinct germ line is lacking in plants and *Hydra*: one somatic cell line is capable of asexual reproduction through “budding,” while also giving rise to germ cells at specific points in time. For Weismann, the indistinction between soma and germ line in self-regenerative plants and animals cannot represent a primordial condition of life (therefore requiring a revision of his theory of germinal heredity), but must have arisen through adaptation. The regenerative power of the lizard’s tail, for example, needs to be understood as an adaptive response to its frequent loss. Not surprisingly, the most extreme representative of this adaptation, according to Weismann, is to be found in the *Hydra*, whose regenerative abilities are so extensive that it is able to completely bypass sexual reproduction.²⁷

Regeneration and Self-regulation—the Critique of Weismann

In light of the marginalization of regenerative phenomena from the defining categories of the germ-plasm theory, it is not surprising that the most cogent contemporary critiques of Weismann revolved around the persistent enigmas of regeneration, self-organization, and epigenesis.

In a series of articles written in the 1890s and a book collection of lectures published in 1901, the embryologist Thomas Hunt Morgan sought to counter Weismann’s growing influence by working toward a comprehensive theory of biological organization, one which could extend to both generation and regeneration, sexual and asexual reproduction.²⁸ In particular, Morgan looked to the dynamic similarities between embryological development and regenerative phenomena as an argument against Weismann’s adaptationist theory of regeneration. On this point, he was inspired by experiments that Wilhelm Roux and Hans Driesch had carried out on the daughter

27. *Ibid.*, p. 185.

28. See T. H. Morgan, *Regeneration* (New York: Macmillan, 1901). For an illuminating and detailed overview of Morgan’s work on regeneration, with full bibliographical information, see Jane Maienschein, “T. H. Morgan’s Regeneration, Epigenesis and (W)holism,” in Dinsmore, *History of Regeneration Research* (above, n. 8), pp. 133–149.

cells or blastomeres of dividing embryos in the 1880s (and to which Weismann had referred, to very different effect). In 1888, Roux killed one of the first few blastomeres of a developing embryo by puncturing it with a hot needle, with the apparent result that the remaining blastomere could produce only a partial embryo. The part, he concluded, could not respond to the modulations of its context: the remaining blastomere could not compensate for the whole, when another was removed; the fate of each cell must therefore be predetermined from within. It was these results that Weismann relied on in his defense of the preformationist view of cellular fate.²⁹

However, Roux's follow-up experiments produced conflicting results, suggesting that a single blastomere could indeed regenerate the whole—a process that Roux defined as postgeneration. These later findings were supported by Driesch's 1892 experiments on sea urchin embryos, demonstrating that when isolated from each other, blastomeres of the two-cell stage developed into complete, though miniature, larvae of normal form. Driesch went on to show that whole larvae could be produced from single cells isolated at the four-cell stage, from eggs whose cleavage pattern had been disrupted, from a single egg divided into two along the meridional plane, and from two eggs fused together. His experiments were later cited as evidence against Weismann's theory of differential nuclear determination. But of more immediate interest to Driesch was the fact that these experiments seemed to point to a self-regulative principle at work in the spatial and temporal organization of morphogenesis. He anticipated the later concept of "positional information" by surmising that the prospective significance (fate) of a cell is a function of its position in the whole, each cell acquiring or losing potency as a consequence of both its relation to other cells and their collective relation to the prospective "whole" of the organism.

It was this notion of the plastic, restorative properties of early embryonic cells that Morgan extended to the problem of self-regeneration in later development. Following up regeneration studies performed by Driesch on the flatworm (planarian), he noted that certain cells contained in the body of the developed animal seemed to be endowed with the "omnipotence" of early embryonic cells, remaining "almost as plastic as that of an undivided or dividing egg."³⁰ In both cases, he suggested, the interacting cells involved in the process of morphogenetic (re)generation were subject to a principle of self-regulation, tending to restore the whole.

29. Weismann, *Germ-Plasm* (above, n. 19), pp. 137–138.

30. T. H. Morgan, "Experimental Studies of the Regeneration of *Planaria maculata*," *Archiv für Entwicklungsmechanik der Organismen* 7 (1898): 364–397, on p. 396.

In this sense, Morgan translates the premises of Kant's canonical formula for self-organization into the language of modern cell theory. Although the potency of the individual cell might be plastic, malleable, open to change as a function of its variable relations to other cells, only one prospective fate is available to cells in their collective interactions—self-regulation within the “whole” of organic form. Morgan himself anticipates a possible critique of his position, when he notes that by making the problem of organization inseparable from the postulate of form, he has perhaps restricted himself to looking for “a causal explanation of form itself,” in which case the problem becomes “insoluble.”³¹ When form is presupposed, he points out, all we can hope to do is delineate the conditions under which a given form appears.

Weismann's Legacy—Forgetting the *Hydra*

It is ironic that Thomas Hunt Morgan, who had so strenuously fought against the preformationist bias of Weismannian theory in his studies on regeneration, would later come to be associated with the classical school of genetics, which would so decisively divorce the question of “transmission” from the problems of morphogenetic organization. In the first decades of the century, when Mendel's laws were rediscovered in light of Weismann's theory of germinal transmission, Darwinian evolution was divested of any residual links to the epigenetic tradition. From 1910 to the late 1920s the classical school of genetics, most closely associated with Morgan and his colleagues, formalized the statistical study of genetic transmission and, in the process, established the foundations of modern genetics by explicitly bracketing off the properly epigenetic questions of ontogeny and cellular dynamics from the domain of heredity. As genetics merged with the new Darwinism, the distance between the epigenetic and preformationist perspectives hardened into a disciplinary standoff.³²

31. T. H. Morgan, “Some Problems of Regeneration,” *Biological Lectures Delivered at the Marine Biological Laboratory of Woods Hole* (1899): 193–207, on pp. 206–207.

32. For a detailed account of Morgan's move from embryology to transmission genetics, and its larger historical significance, see Garland E. Allen, “T. H. Morgan and the Split between Embryology and Genetics, 1910–1935,” in *The Eighth Symposium of the British Society for Developmental Biology: A History of Embryology*, ed. T. J. Horder, J. A. Witkowski, and C. C. Wylie (Cambridge: Cambridge University Press, 1985), pp. 113–146. For more-general accounts of the disciplinary split between classical genetics and embryology, see David J. Depew and Bruce H. Weber, *Darwinism Evolving: Systems Dynamics and the Genealogy of Natural Selection* (Cambridge, Mass.: MIT Press, 1997), pp. 394–395; Michel Morange, *The Misunderstood Gene*, trans. Matthew Cobb (Cambridge, Mass.: Harvard University Press, 2001), pp. 8–14; Keller, *Century of the Gene* (above, n. 17), pp. 11–20.

The ensuing institutional split between embryology and genetics would endure for the greater part of the century, despite the dissenting voices of “developmental geneticists” such as Richard Goldschmidt and C. H. Waddington, who already in the 1940s were calling for an alliance between development, genetics, and evolution. From this point on, the phenomena of regeneration, on which Morgan himself had based his critique of Weismann, became the exclusive concern of the embryologists.

Although the details of Weismann’s model were later reworked (we now know that all cells, including somatic cells, include a full complement of “reproductive determinants,” albeit with differential activity), its fundamental dictates were reiterated by the central dogma of molecular biology in the 1950s, which identified the gene with the self-replicating molecular structure of DNA and defined genetic transmission as the irreversible flow of information from DNA to RNA to protein. In the language of molecular biology, Weismann’s reproductive determinants were replaced by the genetic program or code—a nucleic acid message awaiting its translation into protein.

In a recent work, the theoretical biologist Leo Buss has examined the extent to which the modern alliance between genetics and evolutionism was informed by a “zoological bias” toward experimental models whose mode of reproduction conformed to the categories of Weismannian heredity. He suggests that the choice of the fruit fly *Drosophila* as an almost exclusive experimental model in the period when classical genetics was being elaborated (1910–25) fundamentally inflected the perspective the field would adopt on questions of development.³³ In the taxa to which genetics restricted its attention (diptera, including *Drosophila*, and vertebrates such as mice and humans), the determination of the germ line, in its difference from the somatic cells, occurs very early in development, so that Weismann’s separation of reproduction from developmental (re)generation appears to be closely approximated. This separation, however, is less clear in plants and animals capable of regeneration, as Weismann himself was aware. What this institutional and theoretical bias left aside were those less amenable modes of life—plants, colonial invertebrates, and fungi—that reproduce asexually, through fragmentation, fission, or budding. As Buss remarks, it is at this point that genetic studies of heredity forget the fascinating properties of the freshwater polyp *Hydra*, the developmental model that ushered in experimental embryology in the eighteenth century.

33. Leo Buss, *The Evolution of Individuality* (Princeton, N.J.: Princeton University Press, 1987), pp. 16–24.

Recent work on stem cells, however, has made it possible to account for the asexual reproduction of the *Hydra* in terms other than those prescribed by Weismann's founding distinction between the germ line and soma. In adverse conditions, the *Hydra* does resort to sexual reproduction through the differentiation of germ cells. But otherwise, it is able to multiply itself indefinitely through a process of asexual budding—a process that has been attributed to the fact that it retains a reserve of undifferentiated cells, capable of both renewing themselves indefinitely and replacing all the other cell types of the body. Thus, although the *Hydra* possesses mortal nerve cells that terminally differentiate and die, it is also composed of undifferentiated "interstitial" cells that are effectively immortal, since there is no inherent, internally prescribed end to their capacity for self-division. Since the sixties, these cells have been identified as a kind of "stem cell"—cells that are defined in terms of their regenerative potency (totipotent, multi- or pluripotent, and unipotent).³⁴ In line with Morgan's intuition, the contemporary concept of the stem cell establishes a fundamental connection between the regenerative potency of the early embryonic cell and later phenomena of regeneration.

In animals with low regenerative powers, it is assumed, there is a progressive loss of potency in the course of development. The fertilized human egg, for example, is defined as totipotent, able to give rise, through successive cellular divisions and differentiation, to an entire organism; under some conditions, all of the blastomeres up until the eight-cell stage can do the same. During the blastocyst stage, there is a first restriction of this original totipotency; some of these cells are multipotent or pluripotent—capable of differentiating into many, perhaps all, of the cell types of the body, though no longer able to develop into a whole organism. In later developmental stages, following gastrulation, these cells become differentiated as unipotent stem or precursor cells for some particular cell type.

What makes the *Hydra* so unique, even among self-regenerative animals, is the fact that it never loses the extreme regenerative powers characteristic of multipotent early embryonic cells, allowing it to tirelessly renew all the different somatic cell types of the body. Contemporary stem cell research discovers the *Hydra* as the ultimate

34. The contemporary field of stem cell research should be dated from 1981, when embryonic stem cells derived from mice were first characterized (the isolation of human embryonic stem cells followed in 1998). But the history of this research can be traced back at least two decades earlier, to studies on teratomas (embryonic tumors) and related cancers in mice. I have explored the convoluted history of stem cell and teratoma research in Melinda Cooper, "Regenerative Medicine: Stem Cells and the Science of Monstrosity," *Journal of the Medical Humanities* (forthcoming).

counterexample to Weismann's theory of the germ line, in the sense that its reproduction is entirely indistinguishable from a process of incessant self-regeneration.

Transduction—Rethinking Self-organization

One of the few twentieth-century theorists to have dwelt extensively on the subject of regeneration is the French philosopher of science Gilbert Simondon, who formulates life as a problem of "topological self-constitution," while nevertheless developing an internal critique of the epigenetic tradition.³⁵ Since Aristotle, Simondon contends, the philosophy of epigenesis has been distorted by the fact that it equates the problematic of self-organization with that of "form" or "soul," thereby eradicating the more difficult issues presented by the "lower" life-forms. Here he refers to regenerating coelenterates and worms:

In fact, Aristotle's doctrine, prototype of all vitalisms, stems from an interpretation of life based on the "higher," that is to say totally individuated, species; it could not have been otherwise in an era when the so-called lower species were difficult to observe. If Aristotle takes into account certain species of coelenterates and worms, it is above all in order to discuss the ways in which the soul can inhere in the body, in totality or part by part, in marine annelids capable of regenerating themselves after accidental cutting and whose two segments continue to live.³⁶

In the modern tradition of epigenetic thought, we might extend this critique to Kant, who prematurely resolves some of the more enigmatic capacities of self-regenerative animals within the formal self-organization of the tree. Morgan and Driesch, despite their different scientific vocabulary, remain faithful to the defining limits imposed

35. Although relatively unknown outside France, Gilbert Simondon's work on the relationship between science, technology, and philosophy has exercised an enormous influence on recent French epistemology. His philosophy in many ways preempts the insights of contemporary theories of "emergence" or "self-organization," and this might explain why his work is enjoying something of a revival. For an overview of his work, see the recent collection *Gilbert Simondon: Une pensée de l'individuation et de la technique* (Paris: Albin Michel, Bibliothèque du Collège International de Philosophie, 1994). For a review of his work which also provides an insight into his influence on Deleuze's philosophy, see Gilles Deleuze, "Review of Gilbert Simondon's *L'individu et sa genèse physico-biologique* (1966)," *Pli* 12 (2001): 43–49. An interesting English-language introduction to some of the implications of Simondon's philosophy can be found in Adrian Mackenzie, *Transductions: Bodies and Machines at Speed* (London/New York: Continuum, 2002).

36. Gilbert Simondon, *L'individu et sa genèse physico-biologique* (Grenoble: Jérôme Millon, 1995), p. 168. (All translations from Simondon are my own.)

by Kant's theory of organic life. In the language of late nineteenth-century cell theory, Kantian form is redefined in energetic terms as "the state to which the system tends when it finds its equilibrium: [form] is a resolution of tension," a homeostatic attractor state tacitly guiding the differentiation and determination of cells toward a progressive exhaustion of their potentiality.³⁷ Equilibrium, Simondon writes, corresponds to "the lowest possible level of potential energy," the state in which all productive differences have been canceled out, where no further collective transformation is possible—to this extent, he argues, the postulate of self-regulative equilibrium is incapable of informing a truly generative theory of organization, as Morgan himself had recognized.³⁸ Simondon, on the other hand, proposes to rethink the epigenetic problem of "topological self-constitution" in light of the so-called lower life-forms such as flatworms and *Hydra*, whose powers of regeneration, he suggests, are not so easily accommodated within the limiting conditions of form and stable equilibrium.

Indeed, the entire problematic of self-organization, according to Simondon, needs to be refigured in terms of *information* rather than form, and of *metastable* rather than stable equilibrium.³⁹ *Information*, as he understands it, involves an irreducible element of "disparation": "noise," "fluctuation," or "disequilibrium." Anticipating more recent directions in the sciences of complexity, he argues that a morphogenetic field is able to constitute itself insofar as it incorporates this irreducible element of fluctuation within its own internal structures—or rather, insofar as it is able to organize itself in and through the channeling of this fluctuation.⁴⁰ In Simondon's words, the successive complexification of material structures (whether living or nonliving) can be understood as a "resolution" of this constitutive disequilibrium, a kind of processual problem-solving—although he insists that this is a resolution that never exhausts itself, as long as productive differences are available to it. He describes this as a process of *transduction*: the reticular propagation of structure in far-from-equilibrium conditions; an expansive structuration of differences

37. *Ibid.*, p. 33.

38. *Ibid.*, pp. 24, 211.

39. *Ibid.*, p. 211.

40. In particular, Simondon's philosophy of vital individuation seems to anticipate the work of theorists such as Brian Goodwin and Gerry Webster, who draw on the insights offered by nonlinear dynamics in order to rethink the epigenetic concept of the morphological field. See Gerry Webster and Brian Goodwin, *Form and Transformation: Generative and Relational Principles in Biology* (Cambridge: Cambridge University Press, 1996).

tending toward no limit-point or stable state.⁴¹ “Transduction” defines a mode of self-organization that “resolves” difference creatively, through the invention of its own internal structures, and, at a given level of disequilibrium, is able to pursue its growth while maintaining itself in a state of “metastable equilibrium.” The process of transduction tends toward no definitive resolution of differences, no final point of equilibrium, although it may traverse successive phase transitions defined by the fact that a particular organization of structure is unable to sustain itself at a given level of “metastable equilibrium” and can only survive, as it were, by reorganizing itself otherwise, at another metastable threshold.

It is the crystal that provides Simondon with the simplest example of transduction in the inorganic world. As long as the crystal is maintained in the far-from-equilibrium conditions of an “oversaturated” fluid, he writes, its growth is “indefinite and automatic”: “each of the successive layers of the crystal being able to structure the amorphous field that surrounds them, as long as the field remains metastable; in this way, a crystal is endowed with an indefinite power of growth,” a power which can be “halted” from the outside (if its surrounding field fails to “feed” it with productive disequilibrium), but never inherently “completed,” since in and of itself it tends toward no final equilibrium point.⁴²

If the process of biological self-organization, according to Simondon, also needs to be thought in terms of transduction rather than form, it involves a greater level of topological complexity than inorganic nature. The crystal individuates at the extreme borderline separating interiority from exteriority—its growth can be figured as an iteration, maintaining itself in an eternal present; it cannot remember or anticipate its own complexification. The internal structures of the living being, on the other hand, incorporate memories that co-exist with its present and in turn inflect the future directions toward which it is able to move. In the process, the living being participates in the conditions of its own further complexification. In the course of development, the morphogenetic field not only encounters “problems” from the outside, but must also resolve the creative inflexions engendered by its own process of self-constitution.

It is with reference to the self-regenerative growth of the *Hydra* that Simondon defines the essential premises of biological transduction.⁴³ Writing in the sixties, before the current spate of research on

41. Simondon, *L'individu* (above, n. 36), p. 33.

42. *Ibid.*, pp. 84–85.

43. Simondon discusses the significance of self-regeneration in *ibid.*, pp. 165–187.

stem cells, he notes that the *Hydra* appears to owe its regenerative powers to a reserve of undifferentiated cells that “preserve or recuperate embryonic properties” and “fulfill the role of veritable generative cells,” without being identifiable with Weismann’s sequestered germ cells.⁴⁴ In later textbooks, these cells have been renamed as interstitial cells, because of their dispersal throughout the body, and identified as “pluripotent stem cells”—cells capable of both replacing differentiated, mortal cells and permanently renewing themselves, in an undifferentiated state, through the process of self-division. The remarkable self-regenerative properties of the *Hydra* can be attributed to the fact that its undifferentiated interstitial cells never lose the power of self-division, renewal, and multiple differentiation, effectively immortalizing the plasticity of early embryonic cells. It is for this reason that the *Hydra* never ages—at least as we are accustomed to think of aging. Although it does possess mortal cells, the *Hydra* as a whole is continually regenerated by immortal stem cells that never stop proliferating and migrating throughout the body, replacing cells as they age, terminally differentiate, and die. Hence, “under normal conditions . . . a *Hydra* is dying apically and basally, but is being ceaselessly reborn by the emigration of cells from the growth zone.”⁴⁵ Unique among animals, the *Hydra* is engaged in a process of permanent embryogenesis, for which there is no final point of maturation. In the words of one recent textbook, “*Hydra* is a *perpetual embryo*, and although its terminally differentiated cells die, the cell community survives.”⁴⁶

Paraphrasing Simondon, we might say that the stem cells of the *Hydra* remain perpetually “transducible,” since their actual differentiation into specific tissues never signifies a final loss of potency, a downhill slide into senescence and equilibrium. Their capacity for differentiation is cumulative and proliferative, “far-from-equilibrium,” rather than progressive and totalizing. Moreover, to the extent that the *Hydra* can be said to “reproduce,” it is through a kind of spontaneous extension of its self-regenerative capacities, a morphogenetic amplification through which it reengenders itself in excess of its actual form.

It is the transductive growth of the *Hydra* rather than the self-regulative development of form that, in Simondon’s work, appears as the constitutive principle of the morphological field, and hence

44. *Ibid.*, p. 181.

45. Richard J. Goss, *Principles of Regeneration* (New York/London: Academic Press, 1969), p. 42.

46. Werner A. Müller, *Developmental Biology* (New York: Springer Verlag, 1997), p. 36.

the source and condition of all higher levels of biological complexification. At all levels of organization, he contends, life itself evolves from and continues to incorporate the primordial process of transduction. As a consequence, Simondon invites us to rethink the limits of organic form, as we commonly understand it; to interrogate, in other words, the process of cellular growth, division, and differentiation in light of the most extreme powers of self-regeneration. From this point of view, the stem cells of the *Hydra* can no longer be relegated outside the purview of “normal” cellular fate, but must be taken to represent the extreme possibilities available to *all* embryonic cells, as a function of their relation to other cells.

The question then become: When, if at all, is this potency achieved by human cells in the course of embryogenesis? When and how is it progressively restricted? What are the epigenetic conditions of growth that influence the determination of cell type in the tissues of the developed body? To what extent is this process irreversible?

Reformulated in the language of contemporary developmental biology, these are precisely the questions that inform current research into stem cells. What is at issue, in the theoretical and experimental delimitation of the entity known as the “stem cell,” is the question of cellular potency and the epigenetic conditions of its differentiation and restriction. In the words of one recent textbook introduction, “stemness is not a property but a spectrum of possibilities,” possibilities that can be “tested” only through experimental manipulation.⁴⁷ The question of potency is in turn indissociable from the larger problematic of regeneration. In the words of another textbook:

Why are some animals able to regenerate and others not? What is the origin of the cells that give rise to the regenerated structures? What mechanisms pattern the regenerated tissues and how are these related to the patterning processes that occur in embryonic development?⁴⁸

On Potency, Differentiation, and Limits

If the Kantian principle of formal self-organization has survived in the twentieth-century tradition of epigenetics, it lies not so much in the presumption of form but rather in the implicit limits within which cellular differentiation is thought to be confined.

47. Markus Loeffler and Christopher S. Potten, “Stem Cells and Cellular Pedigrees—A Conceptual Introduction,” in *Stem Cells*, ed. C. S. Potten (London: Academic Press/Harcourt Brace, 1997), p. 1.

48. Lewis Wolpert et al., *Principles of Development* (Oxford: Oxford University Press, 1998), p. 400.

The process of cellular differentiation is commonly envisaged as a progressive restriction of potency, leading from the totipotent fertilized egg and early blastomeres, to the pluripotent cells of the early embryo, and subsequently through a further loss of possibilities as cells follow branching, mutually exclusive pathways of development. Famously, the embryologist Waddington envisages the “epigenetic landscape” of differentiation as a process of “canalization,” leading downhill into a series of separate valleys. A tacit, though by no means essential, consequence of the “canalization,” model is that the progressive restriction of the potency of cells in the course of differentiation is *irreversible*.⁴⁹ The differentiated state of the mature cell is assumed to be stable. In this way, what embryologists since Driesch have defined as the “prospective potency” of the cell is associated with a progressive limitation of its horizon of future modes of being, a downhill slide to a state of final equilibrium.

Studies in regeneration, however, have persistently questioned this model, pointing to cases where a particular state of determination can be suspended, be reversed, or undergo transformation, or where cells remain in a state of indifferentiation characteristic of early embryonic cells.⁵⁰ The specialist in regeneration Hugh Wallace identifies three different processes at issue here.⁵¹ In cases of *transdetermination*, a committed but not yet terminally differentiated cell

49. On the process of “canalization,” see C. H. Waddington, *Principles of Development and Differentiation* (New York: Macmillan, 1967), pp. 46–55. Waddington himself points to exceptions to the rule of epigenetic canalization—including processes of “dedifferentiation” of cells in self-regenerating animals—although he does not revise his model to incorporate these exceptions. My reading of Waddington is indebted to P. W. Andrews, “From Teratocarcinomas to Embryonic Stem Cells,” *Philosophical Transactions of the Royal Society, London* 357 (2002): 404–418.

50. For a sustained theoretical critique of prevailing notions of cellular potency, differentiation, and its limits, see Susan Oyama, *The Ontogeny of Information: Developmental Systems and Evolution*, 2nd ed. (Durham, N.C.: Duke University Press, 2000), pp. 35–37, 220. Oyama notes that recourse to the epigenetic concept of potentiality does not necessarily free us from the presumption of form as a limit to differentiation. The language of cellular potency, she writes, does not detach us from “the notion of fixed limits (often expressed, in fact, as biologically encoded potential). What are limits, in fact, but the boundaries of the range of capacity?” (p. 220n3).

51. Hugh Wallace, “Regeneration,” in Horder, Witkowski, and Wylie, *Eighth Symposium* (above, n. 32), pp. 338–341. For a related discussion, see Oyama, *Ontogeny of Information*, pp. 35–37: she points out that commonly accepted notions of cellular differentiation presuppose that the potency of a cell “narrows with each decision” (p. 36); in the regenerative process of *transdetermination*, on the other hand, “potential seems to shift and *increase* in scope” (p. 37). Any serious consideration of such phenomena, she suggests, would compel us to rethink our dominant conceptions of developmental potentiality.

changes its developmental course. Transdetermination has been observed in the larva of *Drosophila* flies, whose committed imaginal disc tissue will sometimes differentiate into structures characteristic of other discs when it is transplanted. A similar process, called *trans-differentiation* (or *metaplasia*) occurs when already terminally differentiated cells undergo dedifferentiation and develop otherwise. The eye lens of the newt can be regenerated through the dedifferentiation and transdifferentiation of surrounding tissue. The muscle cells of the medusa can also dedifferentiate to produce other cell types, including germ cells. In the final instance, there is the phenomenon of *permanent indifferenciation*, where a reserve of immortal stem cells allows the organism to perpetually renew all its differentiated cell types. The *Hydra* is the paragon of embryonic self-regeneration.

How can these phenomena be accommodated within the prevailing interpretation of cellular differentiation, which tacitly assumes a progressive restriction of potency, leading in the last instance to terminal differentiation and cell death? The problem was already envisaged by the epigeneticist Driesch, who argued that two orders of “prospective potency” needed to be distinguished: one at work in the “normal” process of cell differentiation in embryogenesis, and another to account for the exceptional creative feats of regeneration and asexual reproduction.⁵² Wallace, on the other hand, suggests that the very concept of “prospective potency” needs to be revised so as to incorporate the possibility of transdifferentiation, transdetermination, and indifferenciation. Like Simondon, he wants to rethink the epigenetic problem of topological self-constitution *in light of* the extreme possibilities of self-regeneration. This would lead us to a larger concept of cellular potency—a kind of proto-life—of which the process of restrictive determination would represent one “metastable” actualization among others. The developmental biologist Peter W. Andrews has proposed just such a revision to Waddington’s model of epigenetic “canalization”: he suggests that the determination of cells should not be envisaged as a downhill movement toward irreversible equilibrium, but rather as a provisional stable state which may move through successive transitions in response to changes in the conditions of its epigenetic field.⁵³ On this model, the process of self-organization no longer involves the progressive actualization of form, or even the branching restriction of cellular fate

52. See H. Driesch, *The Science and Philosophy of the Organism*, vol. 1. (London: Black, 1908), p. 84. For a discussion and critique of Driesch’s solution, see Wallace, “Regeneration” (above, n. 51), pp. 340–341.

53. Andrews, “From Teratocarcinomas to Embryonic Stem Cells” (above, n. 49).

toward a multiplicity of stable, equilibrium states, but is refigured in terms of a reticular, proliferative “transduction” which we can never assume to have exhausted its potential for further differentiation.

The fact that such theoretical critiques are becoming increasingly plausible is no doubt related to recent biotechnological experiments in the isolation of the mammalian and human “stem cell,” which have succeeded in provoking powers of dedifferentiation and trans-determination even in the tissues of mammals, and in maintaining the pluripotent cells of the early embryo in a state of permanent, self-renewing indifferenciation. Recent studies, for example, have found that under certain experimental conditions, adult mammalian stem cells, previously thought to be unipotent or pluripotent (able to produce one kind or a restricted number of differentiated cells), are able to dedifferentiate and change into other kinds of differentiated cells. What these experiments have been able to cultivate, through the manipulation of the epigenetic conditions of cellular interaction, are modes of flexible differentiation akin to those at work in the self-regenerating newt or the medusa.

Even more extreme self-regenerative capacities have been “uncovered” in the mammalian embryonic stem cell, derived from the inner cell mass of the developing embryo. The derivation of ES cells separates them from the outermost cells of the original blastocyst—cells that would normally become the placenta and enable the development of the fetus in utero—thus divesting them of the capacity to develop into an embryo. As a consequence of their experimental isolation, the pluripotent cells of the inner cell mass, which would normally undergo a progressive restriction of fate, are maintained in a state of permanent, inexhaustible indifferenciation, allowing them to renew themselves indefinitely while retaining the power to differentiate into any cell type of the body. In the words of one researcher, ES cells are no longer equivalent to the “potential person” in their developmental power.⁵⁴ But what these cells have acquired in the process is another order of potentiality altogether. Unlike the organism from which they have been derived, ES cells reproduce, grow, and regenerate themselves in a state of permanent embryogenesis that precludes the self-regulative organization of form, the coming-into-being of the potential person, and that ultimate limit to organic self-reproduction—senescence. In this sense, their powers of self-organization would be better illustrated by the burgeoning tentacles of the *Hydra* than by Kant’s example of the tree.

54. Roger A. Pederson, “Ethics and Embryonic Cells,” *Science* 280 (1999): 47.

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