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1 Background

What Is a Stem Cell?

The term itself seems to answer the question: a stem cell is a cell that is also a stem. A *cell* is a basic category of living thing, a fundamental "unit of life." A *stem* is a site of growth – an active source that supports or gives rise to something else. Both concepts are deeply rooted in biological thought, with rich and complex histories. The idea of a stem cell unites them, but the union is neither simple nor straightforward. The answer to this opening question unfolds throughout this and the following sections.

Why should philosophers care about stem cells? There are two main reasons. First, stem cells and related phenomena bear on classic biological questions about the nature of development, regeneration, and individuality. These are central topics for philosophy of biology. Second, the ways scientists gain knowledge about stem cells, and the forms this knowledge takes, are unlike those of theory-oriented sciences. So stem cell biology is a rich, relatively untapped source of insights about central ideas in biological thought and about scientific practices and knowledge. The following sections present some of these insights. As a prelude, a brief introduction to stem cell research is appropriate.

Stem cell phenomena – the things stem cell researchers strive to understand – run the gamut from familiar to outré. Among the former are ongoing processes within our bodies: hair grows, skin is shed and replaced, and our cells gradually turn over. These changes are commonplace yet mysterious in their working. Other species exhibit more dramatic regenerative abilities. Starfish and salamanders can replace severed limbs; worms and plants can regrow an entire body from a fragment. Humans' more modest regenerative powers show in wound healing: bones knit, spilled blood is replaced, torn skin and muscle become whole. Such "self-renewing" processes are usually internal and undetected. But over the past century, innovations in ex vivo cell culture have made visible many interior aspects of our embodied experience.[1] Many striking stem cell phenomena occur in transparent artificial bodies of liquid and glass[2]: embryonic stem cell lines, induced pluripotent stem cells, embryoid bodies, organoids, embryo-like structures, and more. These new experimental products offer unprecedented views of heretofore hidden aspects of organismal development, human and otherwise. Their strangeness and artificiality notwithstanding, novel

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[1] Landecker (2007) is an excellent cultural history of the practice and significance of culturing cells. Simian and Bissell (2017) is a more narrowly focused review of ex vivo tissue and organ culture.

[2] Or plastic, but that is less poetic.

stem cell phenomena are created so as to better understand (and control) more familiar ones. Primary among these is the invisible process that carries us from birth to death: *biological development*. Stem cells are the generative stuff of our bodies – the developmental matrix of all multicellular organisms. To understand them is to understand how we are formed, heal, and decline with age. To control them is to control those processes. No wonder the promise of stem cells tends to be overhyped! They are keys to the shape of our lives as living organisms. Of course, we do not understand stem cells fully, and our control over them – at least for now – is extremely modest. Yet what we have learned so far is fascinating and rich in philosophical implications.

Understanding stem cells requires looking carefully at stem cell research practices. Those practices, like much of science today, are very technical and specialized. In addition, stem cell biology presents a further challenge in that it does not include theories, explanations, and abstract models of the sort that philosophers traditionally focus on.[3] Stem cell research has no easily identifiable set of core principles, exemplary methods, or results. Instead, the field presents a sprawling diversity of experimental innovations and achievements, characterized in highly technical ways that make their significance hard for outsiders to appreciate. This experimental character offers a bracing challenge to the philosophy of science: How can we approach such a field and glean philosophical insights from it? This Element takes a particular approach to meeting that challenge, reflected in the organization of its sections. The rest of this section introduces the conceptual background of "cell and stem," along with associated ideas of cell type, division, and lineage. This sets the stage for Section 2, which examines and clarifies the idea of a stem cell: the stem cell concept. That clarification, an abstract model, connects directly to central experimental methods and standards of stem cell biology today. Section 3 discusses these experiments, with further insights about forms of knowledge and progress in stem cell research. Section 4 concludes by examining some important uses of stem cells, both realized and hoped for.

Cells, Cell Types, and Differentiation

First, let's explore some conceptual background, sketching the duality of "cell" and "stem" in biological thought. The term *cell* was introduced to science by Robert Hooke in 1665 – but his meaning was not that of biology today. Hooke was referring to the minuscule empty chambers in slices of cork, revealed by his

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[3] Stem cell research is not unique in its experimental, decentralized, variegated character. Indeed, many areas of life science today are like this, and also relatively neglected by philosophers. Thus some ideas in this book apply beyond stem cells, although my focus here is on that topic.

early forays with the microscope. The study of cells progresses hand-in-hand with advances in microscopy.[4] Hooke, a pioneer of that instrument, intended an analogy with a monk's cell: a small, confined space. The concept of the cell as a living entity came later, codified in nineteenth-century "cell-theory."[5] Theodor Schwann, in *Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants* (1847), states "the proposition, that there exists one general principle for the formation of all organic productions, and that this principle is the formation of cells," together with conclusions inferred therefrom.[6] One such implication is that cells, the elementary units making up an organism's various tissues and organs, must themselves develop in different ways. That is, organismal development involves (or is based on, or consists in) cells undergoing processes of change. Those processes are represented as different paths or tracks: the pathways of *differentiation*. This implication of early cell theory remains a deep background assumption of stem cell research today.

In following the various pathways of differentiation, cells of an organism become different from one another. Some of these differences can be observed with a simple light microscope. Thus, from the mid-nineteenth century onward, scientists have been confronted by observable variety among the cells making up the body of an animal or plant. The prevailing response to such diversity is to classify cells of multicellular organisms into distinct types according to features they have as individuals, such as size and shape.[7] That is, if cells have similar features in their own right, as individual entities observable under a microscope (or otherwise detectable), then those cells are classified as the same type or kind. Advances in microscopy, genomics, and other methods of cell characterization have led to myriad changes in the suite of features used to classify organismal cells into distinct types. But the basic principle of classification remains the same. Today, different cell types are defined in terms of robust, distinct clusters of molecular, biochemical, morphological, and functional traits. The number of cell types in an organism can range from three to hundreds, depending on the species and on how fine-grained a characterization

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[4] See Hacking (1983) for a pioneering discussion of the latter. For historical and philosophical studies of cell biology, see Dröscher (2002), Matlin et al. (2018), and Reynolds (2018).

[5] "The cell theory" is credited jointly to Matthias Schlieden and Theodor Schwann. The history of biological thought on cells is more complex than this brief introduction can indicate; see, for example, Reynolds (2007, 2018) for more detailed treatments.

[6] Schwann (1847, 166).

[7] There are actually two distinct classificatory systems for cells: one for single-cell organisms (microbes) and the other for cells making up the bodies of multicellular organisms. For reasons made clear in the next section, this Element deals only with the latter. See O'Malley (2014), and references therein, for more on microbial classification; and Kendig (2016) for more on classification in the life sciences.

is wanted. In principle, any multicellular organism can be decomposed into a heap of its constituent cells, and those can then be clustered into types and subtypes.[8]

Another idea from early cell theory that has settled into the deep conceptual background of biology today is Schwann's principle of formation: that all cells are produced in the same way. This mode of production is *cell division*: every cell is generated from a parent cell through a process of binary division.[9] Working out the stages of cell division and coordinating these with inherited material localized to chromosomes was a towering achievement of late-nineteenth- and early-twentieth-century biology. Together with breakthroughs on the process of fertilization, studies of cell division yielded a general, universal account of the reproduction and development of all organisms, grounded on the cellular processes of gamete formation (meiosis) and binary division (mitosis).[10] These ideas today operate as background assumptions for many biological fields, including stem cell research. Although rarely stated explicitly, they provide clear criteria for the existence and individuation of cells:

- An individual cell's existence begins with a cell division event (as one of a pair of offspring cells).
- An individual cell's existence ends with either a second division event (producing two offspring) or cell death (and no offspring).[11]

The cell membrane, a universal feature of cells, makes these "conditions of existence" even more precise and clear. Every cell is bounded by an enclosing membrane.[12] This makes for a topological criterion of cell individuality; a cell is

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[8] Cells are not the only constituents of multicellular organisms; nor is cell-level decomposition the only possible or scientifically significant breakdown of these organisms. The idea that a multicellular organism is an assemblage or "society" of cells was prevalent in late-nineteenth-century biology – when key concepts that continue to influence stem cell research were being established (Reynolds 2018).

[9] Consider Rudolf Virchow's dictum: "All cells arise only from pre-existing cells." Of course, this does not answer the question of how the first cell came to be – a question deeply entwined with the origins of life itself. This view of cell division, although highly confirmed and deeply entrenched in current biological thought, emerged out of extensive efforts of discovery and debate (see the essays in Matlin et al. 2018). Schwann's own view, quickly disconfirmed, was that cells coalesce out of structureless cytoblastema in a manner analogous to crystallization or chemical precipitation out of solution.

[10] See, for example, Coleman (1977), Harris (2000), and Matlin et al. (2018).

[11] In sexually reproducing organisms, gamete cells can also fuse to form a new cell: a zygote. However, for reasons that become clear in the next section, stem cell phenomena are limited to divisions that occur within one organismal generation (one organism's lifetime). Thus the complexities of meiosis can be put aside here.

[12] "[M]ore than any other part, the membrane defines the cell, sets its outer boundary, and determines how the cell as an individualized unit interacts with its environment.. . . The membrane binds the cell into a single entity" (Liu 2018, 209). Of course, signals from the environment pass through the cell membrane all the time (and vice versa); the membrane is not a barrier.

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a membrane and that which it bounds. This criterion determines, for any case of interest, how many cells are present. When cells reproduce by division, the process is finished when the membranes pinch off to separate. With such clear conditions for existence and distinctness, cells are perhaps the most straightforwardly countable living things – paradigmatic biological individuals. There is a quite clear and unambiguous way of determining whether an entity belongs to the kind "cell," what sets a cell apart from its environment, and how many cells there are in a given context. So cells are arguably our most straightforward example of a biological individual: a living entity that can be counted, picked out from its environment, and distinguished from other individuals of its kind.[13] Due to these well-characterized general features and clear boundaries, "cell" is a (relatively) well-behaved scientific category (or natural kind, to use the philosopher's term).

Most readers will be familiar with the textbook image of the cell – an idealized model indicating a set of distinguishable parts (organelles) within an enclosing membrane. Such a model depicts shared anatomic features that function in the physiology and metabolism of a (eukaryotic) cell: mitochondria, ribosomes, Golgi apparatus, nucleoli, endoplasmic reticulum, and more.[14] Textbook images of "the plant cell" and "the animal cell" – and perhaps "the prokaryotic cell" – are also fairly well-known. But these familiar images are idealized, generic *models*. Cells "in the wild" are very diverse. As noted previously, the natural kind "cell" subdivides into many more finely individuated kinds: *cell types*. Cells comprising multicellular organisms (the "building blocks" of organisms) are classified into a number of basic cell types, such as neurons, muscle, and blood cells. These, in turn, further subdivide into more finely grained types of neurons, blood cells, and so on.

This background suggests that "the stem cell" is also a cell type – a kind into which some cells of multicellular organisms are classified. Moreover, there are many varieties of stem cells – embryonic, hematopoietic, neural, induced pluripotent, and so on. So we seem to have a generic cell type, "stem cell," subdivided into more specific sub-types, as is the case for neurons and other familiar kinds of cells in multicellular organisms. If so, then we would have

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[13] There is a lively debate in philosophy of biology and beyond about what it takes to be a biological individual (e.g., Guay and Pradeu 2016).

[14] "[C]onsider a typical biology textbook drawing of a cell. In most texts a schematized cell is presented that contains a nucleus, a cell membrane, mitochondria, a Golgi body, endoplasmic reticulum and so on. In a botany text the schematized cell will contain chloroplasts and an outer cell wall, whilst in a zoology text it will not include these items. The cell is a model in a large group of inter-related models that enable us to understand the operations of all cells. The model is not a nerve cell, nor is it a muscle cell, nor a pancreatic cell, it stands for all of these" (Downes 1992, 145).

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already a fairly clear picture of the stem cell concept: a well-behaved natural kind, like the more inclusive kind “cell,” distinguished from other cell types by a defining set of traits. As noted, cell types are defined in terms of traits held by their individual members: cell morphology, biochemistry, metabolism, molecular surface markers, gene expression profile, and so on. However, stem cells are *not* conceptualized and individuated in this way.[15] Cells that are identified as stem cells, of course, have size and shape, gene expression patterns, and other cell traits. But those traits are not what make them stem cells. Stem cells are defined not (only) in terms of the traits they have but by what they can transform into. The concept *stem* does not merely qualify the category “cell” – it introduces another idea altogether.

Stems and Lineages

The term “stem”, in ordinary life, is both noun and verb. A *stem* (noun) is part of a plant, the stalk that supports a flower. To *stem* from something (verb) is to originate from that thing. Both meanings are relevant to the concept of stem (or stemness) applied to cells. A stem is a site of growth – an active source that supports or gives rise to something else. That other thing is, in a sense, primary: a *stem* (noun) plays a supporting role; the object of *stemming* (verb) is that which comes from some origin or source. A stem, conceptualized as a noun or verb, entity or process, is so because of the thing it supports or gives rise to. A stem (or stemming) is powerful, important, and potent – but only relative to something else, not in itself. It is temporally prior but conceptually secondary, to that which it gives rise to. The term *stem cell* (Stammzelle) was coined with exactly these connotations in mind. Ernst Haeckel introduced it in 1868, one of a spate of neologisms associated with his ideas about the Tree of Life (see the next section). The Stammzelle, for Haeckel, referred to the hypothetical origin of all the diverse kinds of cells and organisms – the origin of growth for the phylogenetic tree uniting all living things. Although the meaning of “stem cell” today is not the same as Haeckel’s, his original connotations remain. So the concept of a stem cell is somewhat peculiar, combining two very different ideas. A *cell*, as we have seen, is a well-characterized biological entity, observable via relatively simple technology and clearly distinguished from its environment and other cells by a bounding membrane. A *stem*, in contrast, is the beginning of a process, the point of origin for something that is to be.

This internal tension has important scientific consequences, explored in later sections. One way to manage the tension, reconciling stem cells’ dual aspect, involves another piece of conceptual background: the idea of a *lineage*. In

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[15] The argument for this unfolds across the next two sections.

biology textbooks, a “lineage” is defined as a sequence of biological entities (e.g., organisms, species, cells) linked by ancestor-descendant relations. Only entities that reproduce can form lineages, each an unbroken chain of descent. So the concept of a lineage presupposes some process of reproduction. Boundaries of a lineage are fixed by the chain of inheritance across generations, beginning with an originating ancestor and ending with the last descendants. The association with the notion of a stem, an origin of growth, is obvious. Fittingly, lineages are often depicted as “tree diagrams” that represent generational ties between reproducing entities. Humans are often interested in genealogical relationships, so tree diagrams (in the form of pedigrees) are a familiar representational form. These everyday lineages are of individual persons, each occupying a distinct position in the family tree. In philosophy of science, the most familiar lineages are not of individual persons or organisms but of species: Darwin’s famous sketches of phylogenetic relationships that connect all the diverse forms of living things into a Tree of Life. The nature and definition of biological species is perennially unsettled. The lineage form presumes only that they can stand in ancestor-descendant relations to one another (i.e., that some process of reproduction is involved). In many cases, the process of interest is the reproduction of organisms in populations, which in turn involves the transmission of genes from parent to offspring. Philosophers of science have primarily discussed lineages of this sort, seeking to articulate further constraints that define “units of evolution.” Neto (2019) takes a broader view, arguing that there are multiple kinds of lineages, each corresponding to concepts and practices of different biological research programs (evolutionary, developmental, phylogenetic, etc.). Lineages in stem cell biology tend to support such pluralism.

Any lineage whatsoever can be characterized in terms of its “tree structure” – that is, by features of the graph connecting the point(s) of origin to the most recent descendants (Figure 1). A tree structure consists of

- origin points (no incoming edges);
- end points (no outgoing edges); and
- branch points (one incoming edge, two or more outgoing edges).

A lineage extends from one or more ancestors, through lines of reproductive descent, to one or more end points. The latter may be temporary (the newest generation) or permanent (no more reproduction; the line has ended). The number of origin and end points establishes the boundaries of a lineage. The structure between them consists of some number of generations (e.g., the “depth” of the tree). The simplest such structure is just a linear sequence of entities with no branching. Depending on the manner of reproduction and the entity undergoing it, branch points may be bifurcations or trifurcations; thicker

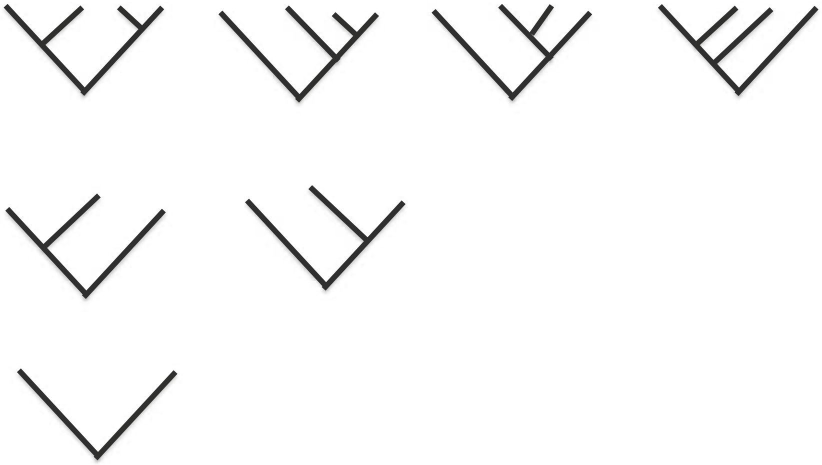

Figure 1 Lineage tree structures

“bursts” are rare. A *cell* lineage consists of successive cell generations, organized by reproductive relations. Because cells reproduce by binary division, cell lineages have a bifurcating tree structure. So the idea of a cell lineage dovetails neatly with tenets of cell theory:

- Cells reproduce by binary division; a parent cell divides to produce two offspring cells.
- Generations of cells linked by reproductive division form a lineage.

Fields that study lineages are interested in not only the pattern of ancestor-descendant chains but also the pattern of variation among the entities so related. For evolutionary biology and phylogenetics, genetic or genomic variation is often of primary importance. Not so for studies of organismal development, however. The lineages of most relevance to organismal development are cell lineages, which exhibit very little genetic/genomic variation. That’s because all the cells comprising a developmental lineage are descended from a single ancestral cell: the zygote.[16] Although some genetic/genomic variability arises over the course of the many cell divisions involved in organismal development, for the most part descendant cells are genetic copies of the original. Of more interest is *epigenetic* variation among cells: changes in gene expression that produce changes in cell structure and function. A key goal of developmental

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[16] Unicellular organisms form lineages through this same reproductive process (cell division). These lineages are at once cell and organism lineages. In multicellular organisms, cell and organism lineages do not coincide in this way. Every living thing originates with a single cell (this includes viruses, albeit in a different way).

biology is to describe the sequence of changes leading to specialized cell types that make up an organism's body.

A Note on Definitions

This section has introduced the conceptual background of stem cell research: interrelated notions of cell, differentiation, cell type, and lineage. The dual nature of stem cells, as clearly bounded biological individuals and protean origins of growth, is reconciled in the figure of a lineage. This gives us a first pass at defining "the stem cell" – as the origin point of a cell lineage. Although on the right track (as the next section argues), this epigrammatic answer is too abstract to fully characterize the stem cell concept as it figures in scientific practice today. This brings us back to the opening question: What is a stem cell? The next section proposes an answer.

As a preliminary to that discussion, a brief note on definitions is needed. Many philosophers are accustomed to definitions as the cornerstone of conceptual analysis – necessary and sufficient conditions for a term or concept to apply. Philosophers tend to prize sparse analytic elegance, a kind of pristine rigor, as the mark of excellence. Many areas of biology do not share this epistemic/aesthetic value, and their products do not exhibit it. Stem cell researchers, like most scientists, do not offer definitions in the way of analytic philosophy. They do introduce new terms, communicate with the general public, and teach novice scientists the meaning of the term "stem cell". All these activities involve a definition, in the working scientist's sense. And these working scientific definitions go some way toward clarifying the concept of *stem cell* – but not far enough to be philosophically satisfactory. The eponymous focal concept of stem cell biology is never explicitly defined in a way that directly reflects that concept's role in scientific practice.[17] Instead, scientists' explicit definitions of "stem cell" are for outsiders and novices. They are therefore simple and abstract, like the textbook model of a generic cell. Hereafter, when I refer to "definitions" of the term "stem cell," I mean, roughly, a conceptual model of that idea. Clarifying the stem cell concept amounts to offering a more nuanced and detailed model of the stem cell concept, and thus offers a clearer window on the practices of stem cell research than the thinner definitions offered by scientists.[18] So the goal of the next section is to bridge the gap between the thin definitions offered by scientists to nonexperts, and the stem cell concept as it figures in scientific practice.

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[17] This may be typical of experimental sciences, though that issue is beyond the scope of this short Element.

[18] Thanks to an anonymous reviewer for pressing me to clarify this point.

2 Stem Cells: The Very Idea

The previous section sketched the dual nature of stem cells, as reflected in their name: clearly individuated biological entities (cells) and generative "springs of life" that give rise to other things (stems). The concept of a cell lineage, with the stem cell as its origin point, encompasses this dual character. But that epigrammatic characterization does not capture the stem cell concept in scientific practice. The next logical step is to look at how stem cells are defined by the researchers who study them. And here we hit a snag. The question "What is a stem cell?" does not preoccupy scientists.[19] They are more concerned with the topics of the next two sections: finding and using stem cells. But the ways they pursue these activities are largely impenetrable to outsiders.[20] Stem cell biology is a complex, untidy, technically challenging, unfinished, and enormously innovative area of science. To engage with it conceptually, without investing in years of training, requires some kind of orienting framework. Lacking such, one is swept away by a sea of technical details, rapidly changing jargon, and unstated assumptions that invite misunderstanding. The idea of a stem cell, being conceptually central for stem cell research, is the natural framework to use. But it will take some philosophical work to articulate it. That is the task of this section.

Of course, this philosophical clarification should be grounded on stem cell science. I begin by dispelling some associations that have accreted into a popular notion of stem cells. After this ground-clearing, I look to the term's historical origin: the German "Stammzelle." The current concept is not the same as the original, yet some key ideas remain. I then turn to present-day definitions of "stem cell" offered by scientists to nonexperts. From this grounding in past and present scientific practice, I articulate a philosopher's definition of "stem cell" – a conceptual anatomy of the concept, which offers a window into stem cell research.

Beyond Embryos

Most readers are probably familiar with the idea of a stem cell, at least in broad outline. In everyday use, the term is closely associated with two other ideas: medical promise and embryo destruction. Both are intensely value-laden, in somewhat opposed ways. On the one hand, stem cells are tokens of medical promise and hope; potential means for curing injuries and diseases ranging from

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[19] Dröscher (2014) argues that, historically, the meaning of "stem cell" is largely tacit, transmitted via metaphor and diagrams (primarily cell lineage diagrams, discussed in this section). This goes for present-day stem cell research too.

[20] Stem cell research is not unique in this respect. Many fields that are experiment-driven have this character, which contributes to the neglect of experiment by philosophers.