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August Weismann's Theory of the Germ-Plasm and the Problem of Unconceived Alternatives[1]

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ABSTRACT - I have argued elsewhere that scientific realism is most significantly challenged neither by traditional arguments from underdetermination of theories by the evidence, nor by the traditional pessimistic induction, but by a rather different historical pattern: our repeated failure to conceive of alternatives to extant scientific theories, even when those alternatives were both (1) well-confirmed by the evidence available at the time and (2) sufficiently scientifically serious as to be later embraced by actual scientific communities. Here I use August Weismann's defense of his influential germ-plasm theory of inheritance to support my claim that this pattern characterizes the history of theoretical scientific investigation generally. Weismann believed that the germ-plasm must become disintegrated into its constituent elements over the course of development, I argue, only because he failed to conceive of any possible alternative mechanism of ontogenetic differentiation. This and other features of the germ-plasm theory, I suggest, reflect a still more fundamental failure to imagine that the germ-plasm might be a productive rather than expendable resource for the cell. Weismann's case provides impressive support for the problem of unconceived alternatives while rendering its challenge to scientific realism deeper and sharper in a number of important ways.

KEYWORDS - Scientific realism, antirealism, unconceived alternatives, pessimistic induction, underdetermination, Weismann, germ-plasm.

Introduction

Challenges to scientific realism (the claim that contemporary scientific theories are at least probably and/or approximately true) have traditionally proceeded in one of two ways: either by appeal to the so-called 'pessimistic induction' inferring the probable falsehood of present

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theories from the demonstrated falsehood of so many of their empirically successful predecessors or by appeal to the underdetermination of theory choice by any possible empirical evidence. The former concern strikes many theorists of science as too simple to be convincing, for contemporary theories are often quite different from those of the past in innumerable particular respects, while devotees of the latter tend to appeal to skeptical fantasies akin to Descartes' famous Evil Demon in a desperate effort to show that there *must* be choices between theoretical alternatives that no evidence could possibly settle.

In recent and forthcoming work (Stanford 2001; in press), I have argued that the most significant challenge to scientific realism does not arise from either of these sources, but instead from our repeated failure to *even conceive of* the full space of serious scientific alternatives well-confirmed by the available evidence before proceeding to embrace just one such alternative by eliminating others. That is, I suggest that the historical record testifies to our repeated failure to conceive of alternatives to the scientific theories proposed at a given time, even when those alternatives were both reasonably well-confirmed by the available evidence and sufficiently serious as to be ultimately embraced by later scientists or scientific communities (i.e. not skeptical fantasies).

Of course, a theory need not accommodate all of the evidence available at a given time to count as well-confirmed, nor need we deny that an older theory can sometimes explain phenomena that a successor cannot or cannot immediately: two theories may simply have *different* explanatory accomplishments and *different* evidential anomalies while both remaining reasonably well-confirmed by the totality of the evidence available at a given time. And if we find that scientists of the past have indeed routinely failed to conceive of serious alternatives that were reasonably well-confirmed by the *totality* of the available evidence, we would have every reason to suppose that similarly serious and well-confirmed alternatives to our *own* best scientific theories remain presently unconceived. Of several advantages over the pessimistic induction, perhaps the most important is that this problem of unconceived alternatives concerns the *theorists* rather than the *theories* of past science: even if contemporary scientific theories sometimes enjoy confirming empirical successes arguably unprecedented in their scope and character, this offers us no reason to suppose that today's theorists are any better at conceiving of the full range of theoretical possibilities confirmed by this evidence than were the greatest scientific minds of the past.

Of course, to decide how serious a challenge is posed to scientific realism by this problem of unconceived alternatives we must engage in a detailed examination of the historical record of scientific inquiry to see if it really does exhibit the pattern I have claimed. In this paper I hope to contribute to this investigation by considering just one important example in the requisite detail: August Weismann's development and defense of his 'germ-plasm' theory of inheritance and generation. My claim is that the details of this development and defense clearly demonstrate Weismann's failure to conceive of serious alternative possibilities that were nonetheless equally well-confirmed by the evidence available to him, and that this in turn supports my suggestion that the problem of unconceived alternatives poses a compelling threat to scientific realism itself.

I choose this example in part because we might expect any positive evidence of the problem we can find in this particular case to be especially revealing. For one thing, the staunch tradition of realism among both scientists and philosophers in the life sciences might naturally suggest that evidence of our historical vulnerability to the problem should be particularly difficult to come by in this arena. Furthermore, as we shall see, recognition of the most consequential alternative line of theorizing neglected by Weismann did not require the development of radically new scientific concepts or any revision of our fundamental ontology (by contrast with, say, the case of some contemporary physical theories). And finally, Weismann's theorizing about inheritance is at least broadly continuous with our own: his theory of the germ-plasm was arguably the last major conceptual development in theorizing about inheritance before the rediscovery (or invention) of Mendel and Mendelian genetics, and his account is directed towards roughly the same collection of phenomena and was articulated under the same broad metaphysical constraints as today's theories of genetics and embryology.

The Emergence of the Theory of the Germ-Plasm

In the latter decades of the 19th century, Weismann faced a very different context of theorizing about generation and inheritance than had any of his illustrious predecessors. Perhaps most importantly, a growing program of research in Germany had followed Ernst Haeckel's early speculation (1866) that the nucleus of the cell was the bearer of hereditary material, and a new generation of microscopical anatomists including Eduard Strasburger, Oscar Hertwig, and Weismann himself had turned their attention in earnest to examining the behavior of the nucleus and chromosomes.[2] Throughout the 1870's and beyond, improved instruments as well as newly developed techniques of immersion, fixation, and staining had rewarded this sustained attention with a rapid pace of landmark discoveries in nuclear cytology. In 1873 Anton Schneider observed the successive stages of mitosis (then called 'indirect' cell division), including the progression of forms taken on by the nuclear elements.[3] In 1875 Hertwig witnessed fertilization in sea urchin eggs, noting that a single spermatozoon enters the ovum and its nucleus joins with that of the egg.[4] In 1879 Walther Flemming published his observations of the longitudinal splitting of the 'chromatin threads' (chromosomes) during mitosis. And in 1883 Edouard van Beneden reported that the process of meiosis involves a 'maturation division' (later termed 'reduction division' by Weismann) producing cells with only half the number of chromosomes found in a non-reproductive cell of the same organism. These findings and others suggested answers and generated new questions even as they galvanized interest in the study of hereditary transmission as such (i.e. distinct from questions about the mechanics of growth, reproduction, and generation more generally).[5] Between 1883 and 1885, prominent German cytologists and experimental embryologists proposed no fewer than five different theories of

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[2] Coleman (1965) offers an extremely useful detailed historical discussion of the developments in cytology described below; see also Churchill (1968, 103f), Robinson (1979, 137-141), and Bowler (1989, 85-87). Note that here and throughout I have tried to restrict my use of the secondary literature concerning this period in the history of science to classic discussions whose central contentions still appear to be widely accepted, rather than to the unavoidably more contentious claims embodied in more recent historical scholarship. As will become clear in what follows, however, the direct evidence I adduce in support of the problem of unconceived alternatives is drawn almost exclusively from primary sources, rather than from this secondary literature. Of course, if more recent developments in the historical scholarship concerning this period undermine either my reading of the primary sources or the use I have made of them in trying to establish the general significance of the problem itself, I trust that my colleagues in the history of science will set me straight.

[3] Although Schneider's results were not immediately well-known, similar observations were soon made by Bütschli, van Beneden, and Fol (see Coleman 1965, 131; Robinson 1979, 137).

[4] While Hertwig reported that the two nuclei fuse in the process of fertilization, the later work of van Beneden would reveal that the respective nuclear contributions from sperm and egg remain intact and discrete (see Coleman 1965, 140-141; Churchill 1968, 106).

[5] As any number of historians have argued and as the remainder of this article will illustrate, however, these dramatic new observations were by no means sufficient to resolve any of the central controversies about inheritance or generation by themselves. Biologists continued to disagree stridently and sometimes vituperatively among themselves about the significance and implications of these cytological findings, and even about what entities and processes had in fact been observed under the microscope. As Bowler notes, it would be 'the growing popularity of the explanatory system which became the basis of classical genetics that at last allowed biologists to agree over the interpretation of their observations' (1989, 86).

inheritance grounded in the notion of some kind of continuity of material structure, not simply from parents to offspring but also within a single organism from early embryogeny to the production of gametes (see Churchill 1987).

One of these was an early version of Weismann's own account, presented in his famous inaugural address to the University of Freiburg in 1883 and published later that same year as the essay 'On Heredity'. It was in this address that Weismann himself first proposed (as Francis Galton had before him) that an organism's germinal materials are sequestered from the beginning of its development and passed directly to that organism's offspring without being affected by events during the course of its life (except for the mixing of such materials required during sexual reproduction).[6] He had not by this point clearly formulated the concept of a germ-plasm, however, and so expressed this germinal continuity as a continuity of the reproductive *cells* from each generation to the next. Weismann conceived of the emergence of multicellular organisms as analogous to the formation of a colony of single-celled organisms, with a division of labor among cells specialized for different functions: most importantly, the germ cells retained the potential immortality of their single-celled ancestors (which had reproduced by simple division) while the cells of the rest of the body (the soma) became simply the evolutionary host and vehicle by which these germ cells were transmitted from one generation to the next. Thus, Weismann's initial formulation of germinal continuity proposed simply that an organism's germ cells are produced by division from its own early embryonic cells and sequestered before the development of its tissues and organs, an arrangement suggested to him by his own earlier work in experimental embryology (see Coleman 1965, 153; Robinson 1979, 153-154; Churchill 1986). Further evidence and criticism would ultimately force him to abandon this position and argue instead that only a germ-*plasm* or hereditary *substance* is reserved from the beginning of ontogeny and passed through a particular series of intervening somatic

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[6] It is important not to exaggerate the extent to which this initial formulation of Weismann's account was itself conceived in reaction to or even constrained by the ongoing developments in nuclear cytology, however: his central concern at the time was instead with problems of evolution and the transmission of characters from parents to offspring (e.g. the inheritance of acquired traits). Indeed, he would later note that when the Freiburg address was written, '...I was not aware that this germ-plasm existed only in the nucleus of the egg-cell, and I was therefore able to contrast the entire substance of which the egg-cell consists, or the germ-plasm, with the substance which composes the body-cells, hence called somatoplasm' (1890, 83). And it was not until the years between 1883 and 1885 that Weismann, Hertwig, and Strasburger would independently focus their attention on the role of the cell nucleus in heredity (see Coleman 1965, 140; Robinson 1979, 141).

cells to the gametes[7] (1885; for discussion see Churchill 1987, 346-347, 352-354). And Weismann's attention was drawn specifically to the nucleus when he became aware of van Beneden's work and realized that the behavior of chromosomes during reduction division and fertilization fit his own theoretical predictions concerning how the germ-plasm must be transmitted (see Bowler 1989, 88).[8]

Weismann's ideas about inheritance and its material foundation, as well as the sequestration of the germ-line, would evolve and develop considerably between 1883 and 1892, the year in which he published his revolutionary landmark: *The Germ-Plasm, A Theory of Heredity* (English translation 1893; hereafter GP). Although this ongoing development would play an important part in undermining the very practice of theorizing about 'generation' – in which the study of hereditary transmission was treated simply as a secondary aspect of the supposedly more fundamental question of how a new organism is manufactured or produced from the material of its parents' bodies (see Bowler 1989, Chs. 2-4) – the fully mature theory Weismann himself produced was nonetheless remarkable for its comprehensive and synthetic character: it sought to account for the phenomena of growth, development, reproduction, regeneration, and ontogenetic differentiation in addition to those of hereditary transmission.[9]

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[7] Weismann reports that he came to this belief in the continuity of the germ-plasm under the impression that the theory was entirely original, but later discovered that 'similar ideas had arisen, in a more or less distinct form, in other brains' ([1892] 1893, 198). Most notably, he allows that Galton's ideas 'bore some resemblance to the conception of the continuity of the germ-plasm', but nonetheless insists that there are crucial differences between his own proposal and Galton's, perhaps most importantly that his own version of the idea does not depend upon a 'residue' left over after hereditary particles are selected for development, but instead 'is founded on the view of the existence of a special adaptation, which is inevitable in the case of multicellular organisms, and which consists in the germ-plasm of the fertilized egg-cell becoming doubled primarily, one of the resulting portions being reserved for the formation of germ-cells' ([1892] 1893, 200).

[8] Most famously, Weismann had predicted the need for reduction division in the formation of sex cells on the basis of purely theoretical considerations. He would not, however, immediately accept van Beneden's suggestion that this reduction was effected in egg cells by the expulsion of the polar bodies, interpreting the latter event instead as the removal of a special 'ovogenetic idioplasm' (see Weismann 1885; 1887; and Churchill 1968, 106-108).

[9] This was perhaps a natural consequence of Weismann's unique position at the intersection of evolutionary theory and cytology (see Bowler 1989, 84f), where he combined 'the points of view of the microscopical anatomist, the embryologist, and the evolutionist' (Coleman 1965, 152). Indeed, as an anonymous *HPLS* referee was right to stress, although Weismann presents his theory of the germ-plasm in GP as an account of heredity and development, the theory played an important role in his work more broadly in advancing particular views concerning evolution. And it is not unreasonable to suppose that the constraints imposed by this intended role in evolutionary theorizing played some part in Weismann's failure to conceive of particular alternatives to the theory of the germ-plasm itself (see below).

The impact of this mature theory would also ultimately prove to be the undoing of the then-dominant developmentalist tradition of theorizing about these questions, which conceived of heredity by means of a vague analogy with memory and treated embryological development itself as a model for a quite general tendency in nature for vital or teleological forces to push natural processes to ascend towards higher levels of complexity, organization, or perfection (see Bowler 1989 Ch. 2). This developmentalist perspective was perhaps most famously captured in the claim of Haeckel's 'biogenetic law' that in the course of its embryological development each individual organism is successively conveyed through the *adult* forms of the various preceding organisms in the evolutionary history of its species and thus that 'ontogeny recapitulates phylogeny'. Ironically, however, historians of the period have argued convincingly that the development of Weismann's own account relied on the notion of ontogenetic recapitulation and was thus itself firmly grounded *within* the developmentalist tradition whose doom it foretold (Churchill 1986 passim; Bowler 1989, 87; Gould 1977, 102-109). Moreover, the emergence of Weismann's distinctive account of inheritance and development from this foundation was itself an intricate and piecemeal process, as he came only slowly to reject Haeckel's conception of reproduction as a kind of 'overgrowth' or excess production of the parent's own tissues,[10] as well as Schwann and Haeckel's reductionist conception of such growth as a process analogous to the formation of inorganic crystals by accretion, not to mention his own earlier steadfast commitment to epigenesis (see Coleman 1965, 151-154; and esp. Churchill 1968). In their place he came to embrace the idea that development and inheritance would have to be explained by the transmission of discrete nuclear elements in a continuous germ line from ancestors to offspring, consisting of fundamental vital particles whose hereditary influence on an individual organism was somehow predetermined by and encoded in their respective heterogeneous material constitutions.

An important part of what prompted Weismann to develop the clear and comprehensive statement of his views offered in *The Germ-Plasm* was the publication in 1889 of a brief, challenging work on inheritance and generation entitled *Intracellular Pangenesis* by the

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[10] Haeckel argued, that is, that reproduction simply reflected the separation and continued growth of surplus material from the parents' own body or bodies, and thus that 'reproduction is a maintenance and a growth of the organism over and beyond the individual mass, one part of which is elevated to the whole' (Haeckel 1866 II 16; cited in Churchill 1968, 97).

botanist Hugo de Vries. Although Weismann embraced central elements of de Vries's account and it may have precipitated his own final break with epigenesis (see Churchill 1968, 105-106), Weismann was also concerned in *The Germ-Plasm* to clarify crucial outstanding differences between de Vries's views and his own and to defend his commitments on these matters (see Robinson 1979, Ch. 8). Among these differences were de Vries's denial of the need for a reduction division and of any important distinction between somatic and germ tracks (as well as his related belief in the totipotency of all or most somatic cells), but perhaps most important of all was Weismann's insistence that the hereditary material must exhibit a precise hierarchical internal *structure* (as against de Vries's conception of his 'pangenes' as freely mixing independent entities; see Weismann 1893, Ch. 1 Sec. 4, esp. p. 69). On Weismann's account, the germ-plasm as a whole consisted of smaller constituent units called *idants*, which Weismann identified (probably but not certainly) with the *chromosomes* visible under the microscope. These idants were themselves composed of *ids*, each of which contained individually a sufficient amount and variety of hereditary material to produce a complete organism of the relevant species.[11] The ids were in turn made up of *determinants*, each responsible for directing the development and operation of either a single cell or multiple cells of a single uniform kind.[12] Finally, these determinants were themselves composed of Weismann's *biophors*, the fundamental vital particles noted above (comparable to de Vries's 'pangenes' – as Weismann acknowledged [Weismann 1893, 42] – or Hertwig's 'idioblasts'), each responsible for determining a particular characteristic of a particular cell. These biophors were themselves capable of assimilation and metabolism, growth, and multiplication by fission (albeit in virtue of their physico-chemical constitutions; see Weismann 1893, 37-45), and to account for the diversity of cellular types and characteristics found in the organic world Weismann supposed that they could exist in a nearly unlimited variety of forms produced by differences in the identity and arrangements of their underlying molecular constituents. And despite the fact that they could not be seen under the

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[11] Weismann also finds it 'probable that the ids correspond to the small granules hitherto called 'microsomata,' which are known to form the individual idants in many animals' (Weismann 1893, 67; see also 1893, 240-241).

[12] Though Weismann allowed that even large groups of identical cells might be represented in the germ-plasm by just a single determinant, any two cells capable of independently heritable variation would have to be represented in the germ-plasm by distinct determinants (Weismann 1893, 53-57).

microscope, Weismann did not regard the existence of such fundamental vital particles as in any way speculative or uncertain:

> *The biophors are not, I believe, by any means mere hypothetical units; they must exist*, for the phenomena of life must be connected with a material unit of some sort. But since the primary vital forces – assimilation and growth – do not proceed spontaneously from either atoms or molecules, there must be a unit of a higher order from which these forces are developed, and this can only consist of a group consisting of a combination of dissimilar molecules. I emphasize this particularly, because a theory of heredity requires so many assumptions which cannot be substantiated that the few fixed points on which we can rely are doubly valuable. (Weismann 1893, 44, original emphasis)

On Weismann's account, then, the continuity of the germ-plasm does not simply consist in a swarm of biophors being reserved from the beginning of ontogeny and then passed from parent to offspring (see esp. Weismann 1893, 64-66). Each biophor in each determinant is a candidate to play a very specific role in the cellular economy of a given type of organism; thus, the reduction division of meiosis does not simply divide the hereditary materials at random, but instead selects a particular *complement* of biophors, hierarchically structured into determinants, ids, and idants, for inclusion in a given sex cell. And while the germ-plasm of any given organism consists of innumerable fragments copied from the 'ancestral germ-plasms' of its various forebears (each having persisted through the reduction division of each preceding generation of sexual reproduction to be passed down through a reproductive cell in one of the organism's own parents), the mechanics of reduction division ensure that any complete germ-plasm formed by uniting these ancestral fragments to those of another sex cell (as well as the sex cells generated from it in turn) will retain a constant proportion of the specific hereditary materials required for the formation of each part of the organism and for each stage of its ontogeny.

But it was not only nor even primarily to ensure the appropriate distribution of these precisely differentiated hereditary materials in reproduction that Weismann attributed a complex structure to the germ-plasm. Weismann embraced Wilhelm Roux's controversial claim (1883; see Coleman 1965, 141-142, 152) that as new cells are formed by division in the course of ontogeny the germ-plasm must itself be divided not only quantitatively but also *qualitatively*. That is, according to what would become known as the Roux/Weismann doctrine, the nuclei of the two cells resulting from cell division in ontogeny typically received *different parts* of the organism's germ-plasm.[13] And Weismann argued that the primary function of the overarching hierarchical structure of any organism's germ-plasm was to ensure that the right components of the hereditary material became available and activated in the right cells at the right time as it underwent these sequential qualitative divisions.

On Weismann's account, then, the fertilized egg's *own* germ-plasm would be divided in each ontogenetic cell division (each 'onto-idic stage'), with qualitatively different portions of the germ-plasm passed on to the various cells destined to generate distinct parts of the body. Thus, an organism's hereditary material was progressively separated into its constituent elements as it directed ontogenetic differentiation and cellular function, and Weismann adopted Nägeli's term 'idioplasm' to describe the hereditary substance in this active ontogenetic role (that is, once designated for the control and development of somatic cells and located in their nuclei, with no chance to share in the potential immortality of true germ-plasm). He reserved the term 'germ-plasm' (whenever the contrast was relevant) to describe intact, complete *copies* of the germ-plasm of the fertilized egg, produced at the beginning of ontogeny and destined to migrate in an inactivated, unalterable state along a specific developmental path into the reproductive cells. This required Weismann to recognize two different (but experimentally indistinguishable) kinds of nuclear division: *homœokinesis*, characteristic of the reduction division required for sex cells, in which the germ-plasm is developed into parts that are structurally identical with respect to their hereditary tendencies, and *heterokinesis*, characteristic of ontogeny, in which the germ-plasm or idioplasm is divided into heterogeneous parts with very different hereditary tendencies. In each ontogenetic cell division into a new onto-idic stage, then, the idioplasm would itself be reduced, although it would not be exhausted by such cell divisions because it would continue to grow throughout the life of the organism (at least while or for any part of the organism in which the cells retained the ability to divide).

Weismann was alone or nearly so in embracing Roux's suggestion that the ontogenetic division of cell nuclei was qualitative as well as quantitative: virtually all of his contemporaries instead followed van Beneden in holding that cell division simply involved a quantitative division and distribution of identical hereditary materials to the two daughter cells. But it would be a mistake to view Weismann as having

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[13] Although Roux originally proposed the notion that the quantitative division of nuclear material in cell division was also a qualitative division in 1883, Weismann would not credit Roux with this idea until 1887 (see Churchill 1968, 103n).

merely endorsed a suggestion about cell division in ontogeny (and proposed a corresponding structure for the germ-plasm) that failed to pan out. Instead he argued explicitly and repeatedly that there simply was *no possible alternative* to the view that the germinal materials were separated in each ontogenetic cell division until each cell retained only the specific hereditary materials needed to determine its own characteristics. And as the next section will illustrate, it is in Weismann's emphatic insistence on this position in the face of what seemed to his contemporaries to be decisive contrary evidence from cytology and embryology that we begin to see evidence of his failure to conceive of important alternative theoretical possibilities.

Germinal Specificity, Germ-Plasm Reservation, and the Search for a Mechanism of Cellular Differentiation

Weismann was among the first to propose an account of heredity on which germinal materials *controlled* the development and characteristics of the cells they inhabited, but did not themselves *become* the cells, tissues, or other features of the organism whose development they directed. But his conception of just *how* a particulate hereditary material might exercise this directive function was far from being a simple approximation or less detailed version of our own, a fact reflected in his engagement with the further question of whether the hereditary material is the same or different in the various constituent cells of an organism. He returns repeatedly to this issue in *The Germ-Plasm*, always to insist unequivocally that the nuclei of different cells *must* contain different constituent elements of the organism's hereditary material, a view of the matter that we might call *germinal specificity*.

At first blush, Weismann's insistence on germinal specificity is somewhat puzzling: after all, observations of chromosomal behavior in the nucleus had never suggested any differences between the nuclear materials passed to each daughter cell during ordinary cell division, and every somatic cell appeared to wind up with the same amount of chromatin.[14] But Weismann concedes these empirical facts while brushing them aside as inconsequential:

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[14] Indeed, other theorists (e.g. Kölliker, Strasburger; see Robinson 1979, 151-154 and 159-160) would argue that Weismann's insistence on germinal specificity and an important difference between the germ-plasm contained in various cells (e.g. germ cells and soma) was *cytologically* implausible.

> It is quite true that the idioplasm of such cells appears similar, at least we can recognize no definable differences in the chromatin rods of two cells in the same animal. But this is no argument against the assumption of an internal difference. The perfect external resemblance between two eggs is not a sufficient reason why two identical chickens should be hatched from them. We cannot perceive these slight differences in either case, and we could not even do so by attempting to analyse the idioplasm concealed in the nuclei of the two eggs by the aid of our most powerful objectives. Theoretical considerations will show later on that it must be so....We shall consequently in this connection have to assume two kinds of nuclear division which are externally indistinguishable from one another, in one of which the two daughter-nuclei contain similar idioplasm, while in the other they contain different kinds of idioplasm. (Weismann 1893, 33-34).

Weismann was surely right to suggest that the failure to detect any difference under the microscope between the nuclei of somatic cells in the same organism did not *rule out* the possibility that such differences existed nonetheless. But how could he be so sure that there *must be* such a difference? What 'theoretical considerations' produced such confidence in the absence of any supporting observational or experimental evidence?

The primary consideration to which Weismann appeals in arguing for the necessity of germinal specificity is the simple fact that different cells develop differently over the course of ontogeny and ultimately come to exhibit different characteristics:

> The question now arises as to whether all these fragments of the hereditary substance...are similar to, or different from, one another, and it can easily be shown that the latter must be the case....As the thousands of cells which constitute an organism possess very different properties, the *chromatin* which controls them *cannot be uniform; it must be different in each kind of cell.* The chromatin, moreover, cannot *become* different in the cells of the fully formed organism; the differences in the chromatin controlling the cells must begin with the development of the egg-cell, and must increase as development proceeds; for otherwise the different products of the division of the ovum could not give rise to entirely different hereditary tendencies. This is, however, the case. Even the two first daughter-cells which result from the division of the egg-cell give rise in many animals to totally different parts....The conclusion is inevitable that the chromatin determining these hereditary tendencies is different in the daughter-cells. (Weismann 1893, 31-32, original emphasis; see also Weismann 1893, 61)

Likewise, Weismann later argues that the very possibility of ontogenetic development and cellular differentiation depends on the capacity for changes in the controlling idioplasm:

> The idioplasm...is capable of regular change during growth; and ontogeny, or the development of the individual in multicellular organisms, depends upon this fact. The two first embryonic cells of an animal arise from the division of the

> ovum, and continually give rise to differently constituted cells during the course of embryogeny. The diversity of these cells must, as I have shown, depend on changes in the nuclear substance. (Weismann 1893, 45)

Thus, it is first and foremost the simple fact that in the course of an organism's development its various cells come to have very different forms and characteristics that Weismann takes to require germinal specificity.[15] But this seems simply to push our original question back one step. That is, we must now ask how Weismann could be so sure that cells must contain different parts of the hereditary material if their respective courses of ontogenetic development are to diverge.

An important clue to answering this question can be found in Weismann's insistence that it must be by means of the *gradual disintegration of the germ-plasm* that different cells come to contain different germinal materials over the course of ontogeny:

> In my opinion, it is also an irrefutable fact that this germ-plasm undergoes regular changes from the ovum onwards: it must, indeed, undergo change from cell to cell, for we know that the individual cell is the seat of the forces which give rise collectively to the functions of the whole. The forces which are virtually contained in the germ-plasm can therefore only become apparent when its substance undergoes disintegration, and its component parts, the determinants, become rearranged. The difference in function seen in the various groups of cells in the body compels us to suppose that these contain a substance which acts in various ways. *The cells are therefore centres of force of different worth, and the substance (idioplasm) which controls them must be just as dissimilar as are the forces developed by them.* (Weismann 1893, 204, original emphasis)

Elsewhere Weismann provides a more complete description of this process of the disintegration of the germ-plasm and how it ensures that each cell is provided with precisely the germinal elements needed for its own development. Central to this proposal is the idea that cell divisions separate the idioplasm into simpler and more basic constituent elements:

> As the greater number of these divisions is connected with a diminution in the number of kinds of determinants, the geometrical figure representing the id gradually becomes simpler and simpler, until finally it assumes the simplest

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[15] This argument for germinal specificity appears in Weismann's work at least as early as 1885: 'I therefore believe that we must accept the hypothesis that, in indirect nuclear division, the formation of unequal halves may take place quite as readily as the formation of equal halves, and that the equality or inequality of subsequently produced daughter-cells must depend on that of the nuclei' (1885, 193).

> conceivable form, and then each cell will contain the single kind of determinant which controls it. The disintegration of the germ-plasm is a wonderfully complicated process; it is a true 'development', in which the idic stages necessarily follow one another in a regular order, and thus the thousands and hundreds of thousands of hereditary parts are gradually formed, each in its right place, and each provided with the proper determinants.
>
> The construction of the whole body, as well as its differentiation into parts, its segmentation, and the formation of its organs, and even the size of these organs, – determined by the number of cells composing them, – depends on this complicated disintegration of the determinants in the id of germ-plasm. *The transmission of characters of the most general kind – that is to say, those which determine the structure of an animal as well as those characterizing the class, order, family, and genus to which it belongs – are due exclusively to this process.* (Weismann 1893, 68-9, original emphasis)

Thus it is by the progressive disintegration of the germ-plasm, Weismann argues, that germinal specificity is achieved and that individual cells come to contain the specific elements of the hereditary material appropriate to their functioning and ontogenetic fate.

The significance of this claim becomes apparent once we appreciate the close connection Weismann sees in *The Germ-Plasm* between the question of how the idioplasm is distributed to the respective individual cells of an organism and that of how it achieves and maintains control over each of those cells, for the progressive disintegration of the idioplasm turns out to be the crucial mechanism at work in both of these processes. Concluding the first section of Chapter 1, Weismann reminds us that the 'capacity on the part of the idioplasm for regular and spontaneous change' is 'beyond doubt, when once it is established that the morphoplasm of each cell is controlled, and its character decided, by the idioplasm of the nucleus', and closes with a question: '*But what is the nature of these changes, and how are they brought about?*' (Weismann 1893, 45, original emphasis). The first sentence of the following section (entitled 'The Control of the Cell') assures us that 'In order to answer the question which has just been asked, it will be necessary to consider the manner in which the idioplasm of the nucleus determines the characters of the cell' (Weismann 1893, 45).

In this section Weismann takes up and defends de Vries's suggestion that nuclear control of the cell must be mediated by the passage of material particles from the nucleus into the surrounding cytoplasm.[16] And he later goes on to argue that this mechanism for

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[16] More fully, Weismann argues that if the idioplasm is to 'exert a determining influence' over the cell, 'it must either be capable of exerting an emitted influence ('*Fernwirkung*') or else material particles must pass out of the nucleus into the cell body' (Weismann 1893, 45). But he argues that

achieving nuclear control of the cell simply *requires* the disintegration of the idioplasm into its constituent elements:

> We have now seen by what means the biophors characteristic of any particular cell reach that cell in the requisite proportion. This results from the fact that the biophors are held together in a determinant which previously existed as such in the germ-plasm, and which was passed on mechanically, owing to its ontogenetic disintegration, to the right part of the body. In order that the determinant may really control the cell, it is necessary that it should *break up into its constituent biophors*. This is an inevitable consequence of the assumed mode of determination of the cell. We must suppose that the determinants gradually break up into biophors when they have reached their destination. This assumption allows, at the same time, an explanation of the otherwise enigmatical circumstance, that the rest of the determinants, which are contained in every id except in the last stages of development, exert no influence on the cell. (Weismann 1893, 69-70, original emphasis)

Here Weismann insists in no uncertain terms that the nuclear idioplasm cannot possibly control the development and differentiation of the cell unless it disintegrates into its constituent material elements. And he maintains this insistence even as he goes on to emphasize our ignorance of the details of the internal structure of the hereditary material itself:

> As each determinant consists of many biophors, it must be considerably larger than a biophor, and is probably therefore unable to pass out through the pores of the nuclear membrane, which we must suppose to be very small and only adapted for the passage of the biophors. Although it is impossible to make any definite statement with regard to the internal structure of the determinants, it must be owing to this structure that each determinant only breaks up into biophors when it reaches the cell to be determined by it. We may suppose that, just as one fruit on a tree ripens more quickly than another, even when the same external influences act on both, so also one sort of determinant may mature sooner than another, although similar nourishment is supplied to both... The assumption of a 'ripening' of the determinants...remains indispensable; or, to express it differently, we must assume that the determinants pass through a

the first possibility would require the structures of living cells to come into existence by 'a kind of *generatio_equivoca*' in which 'they would have arisen by the operation of an external influence on the given substance in the cell, just as would be the case in primordial generation'. And Weismann insists not only that such primordial generation is unknown in 'those forms of life with which we are acquainted', which 'always arise by division from others similar to themselves', but also that '[w]e can only imagine the very simplest biophors as having been produced by primordial generation: *all subsequent and more complex kinds of biophors can only have arisen on the principle of adaptation to new conditions of life*' (Weismann 1893, 47-48, original emphasis). Thus 'the structures of a cell-body, which constitute the specific character of the cell, cannot be produced by the emitted influence of the nuclear substance, nor by its enzymatic action, but can only arise owing to the migration of material particles of the nucleus into the cell-body' (Weismann 1893, 48-49, original emphasis).

> strictly regulated period of inactivity, at the close of which the disintegration into biophors sets in. (Weismann, 1893, 70)

A few pages later Weismann goes on to insist that the 'facts with which we are acquainted' render 'unavoidable' the assumption that the germ-plasm can exist in either an 'active' or 'inactive' state, and simply *defines* the difference between them as consisting in the fact that the former 'become disintegrated into their constituent parts' while the latter 'remain entire, although they are capable of multiplication' (Weismann 1893, 74-75).

We thus arrive at an answer to our original question about Weismann's confidence in the need for germinal specificity: cellular differentiation over the course of ontogeny absolutely requires germinal specificity by Weismann's lights because he believes that the hereditary material can exert control over the cell only by disintegrating into its constituent elements and that such disintegration can produce cells with different characteristics only if the constituent elements making up the hereditary material in those cells are themselves distinct. That is, Weismann believes not only that the progressive disintegration of the germ-plasm into diverse constituent elements is in fact the process by which germinal specificity is achieved, but also that this is the only possible mechanism by which the germ-plasm could control the cell from within the nucleus to produce the kind of cellular differentiation actually observed over the course of ontogeny.

It would be a mistake, however, to suppose that Weismann simply never managed to conceive of any alternative to germinal specificity itself, for the possibility that the *entire* complement of germinal material is duplicated and passed on to each cell of the body in cell division was in fact the view of such important contemporaries as de Vries and Hans Driesch. And indeed, Weismann himself gives clear and elegant expression to this alternative in the course of rejecting it:

> The regularity with which all organs are formed in the proper position and mutual relation, may perhaps be taken as a proof of the assumption that they contain latent determinants which are from the first separate, and which differ according to the topographical position of the organ. It is hardly possible that the contrary assumption can be the correct one, for this would render it necessary to suppose that although all the determinants are certainly present in every formative cell, only that one can undergo development which corresponds to the region in which the cell happened to be situated. (Weismann 1893, 150)

Having so clearly conceived of the idea that the entire germ-plasm is reproduced at each cell-division and contained in the nucleus of each somatic cell of an organism, how could Weismann so confidently dismiss this possibility out of hand? As his more detailed criticisms of de Vries and Driesch make clear, it was because he found it absolutely impossible to conceive of any effective mechanism of ontogenetic development and differentiation that could permit the same hereditary material to reside in the nucleus of each somatic cell.[17]

As we noted above, Weismann endorses a number of de Vries's central claims about heredity from *Intracellular Pangenesis*, including most importantly the proposal that nuclear control of the cell must be mediated by the passage of material particles from the nucleus to the surrounding cytoplasm (Weismann 1893, 46-47, 69). But he insists that it is a profound mistake for de Vries to deny germinal specificity, as this would undermine the very possibility of explaining the ontogenetic differentiation of cells:

> De Vries, on the other hand, considers that the whole of the primary constituents of the species are contained in the idioplasm of every, or nearly every, cell of the organism. But he does not explain how it is that each cell nevertheless possesses a specific histological character. A new assumption, which would not be easy to formulate, would therefore be required to explain why only a certain very small portion of the total amount of idioplasm – which is similar in all parts of the plant – becomes active in each cell. (Weismann 1893, 223; cf. Weismann 1893, 69)

Weismann was well aware that it was processes like regeneration and reproduction by budding in plants which led de Vries to suppose that the entire germ-plasm must be present in every cell. But he insisted that ontogenetic differentiation nonetheless requires different constituents of the hereditary material to be present in different cells, with additional partial or complete copies of the idioplasm (in an inactivated state) invoked as a special adaptation and made available only to particular cells of an organism as needed to explain the

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[17] Elsewhere Weismann dismisses this possibility more offhandedly by suggesting that it violates the principle that 'Nature...always manages with economy' (Weismann 1893, 63), but this would seem to be a secondary consideration. Not only is Weismann's explicit argument that ontogenetic differentiation requires different cells to contain different hereditary materials considerably more developed and fundamental, but (as we will see below) Weismann is ultimately forced into a drastic multiplication of unused and inactive partial or complete copies of the germ-plasm to accommodate a wide variety of forms of facultative responsiveness that cells exhibit to their environments, which makes his selective appeal here to the economy of nature look suspiciously opportunistic.

abilities of particular parts of organisms to regenerate or to reproduce asexually:[18]

> [My] theory explains the differentiation of the body as being due to the disintegration of the determinants accumulated in the germ-plasm, and requires a special assumption, – viz., that of the addition of accessory idioplasm when necessary, – in order to account for the formation of germ-cells, and the processes of gemmation and regeneration. The reconstruction of entire plants or of parts from any point can be easily accounted for by de Vries's hypothesis, just as it can by Darwin's theory of pangenesis, for the pangenes or gemmules are present wherever they are wanted. But de Vries is unable, on the basis of his hypothesis, to offer even an attempt at an explanation of the *diversity* of the cells in kind and of the *differentiation* of the body.
>
> These two assumptions appear to me to be of equal value in explaining the fact that in many of the lower plants each cell, under certain circumstances, can apparently reproduce an entire individual... But ... as soon as the soma can become variously differentiated ... any explanation must in the first place account for this differentiation: that is to say, the diversity which always exists amongst these cells and groups of cells arising from the ovum must be referred to some definite principle. De Vries's principle is of no use at all in this case, for it only accounts for the fact that entire plants may, under certain circumstances, arise from individual cells, and does not even touch the main point. In fact, no one could even look upon it as giving a partial solution of the problem, if differentiation is supposed to be due to that part alone of the germ-plasm always becoming active, which is required for the production of the cell or organ under consideration. [19] (Weismann 1893, 223-224)

Why is Weismann so confident that no explanation of differentiation will be forthcoming on de Vries's assumption that the entire idioplasm is present in the nucleus of each somatic cell? Why, that is, is he so sure that a 'further assumption' capable of explaining cellular

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[18] And Weismann repeatedly emphasizes that regeneration or budding can only be initiated from *some* cells of an organism and not others – a fact which he regards as further evidence for germinal specificity.

[19] In the secondary literature, differences between Weismann and de Vries are often ascribed to the fact that Weismann was a zoologist while de Vries was a botanist and each was most impressed and concerned with the hereditary phenomena characteristic of the types of organisms that he had studied most closely (see e.g. Robinson 1979, 175; Bowler 1989, 91). It is therefore interesting to see Weismann here explicitly describing his own account as *equally* able to explain characteristic botanical phenomena like budding, as well as better able to explain the phenomena of cellular differentiation, and going on to suggest that de Vries is but he himself is not a victim of the professional provincialism implicit in this contrast: 'But the higher we ascend in the organic world, the more limited does the power of producing the whole from separate cells become, and the more do the numerous and varied differentiations of the soma claim our attention and require an explanation in the first instance... In the lower plants the fact of the differentiation of the soma is liable to be overlooked or underrated, but this cannot possibly be the case as regards the higher animals' (Weismann 1893, 224). Interestingly, de Vries makes a similar accusation in the reverse direction regarding modes of reproduction in *Intracellular Pangenesis* ([1889] 1910, 81).

differentiation without germinal specificity or the disintegration of the germ-plasm 'would not be easy to formulate'? To answer this question we will have to consider Weismann's response to an influential series of experiments performed in 1891 by Hans Driesch with newly fertilized eggs of sea urchins, for it is in the course of this response that Weismann argues explicitly that *no* conceivable mechanism of ontogenetic differentiation could allow precisely the same hereditary material to be present in the nucleus of each somatic cell.

Weismann discusses Driesch's experiments in the context of defending the 'self-differentiation' of cells; that is, the view that cellular differentiation and development are controlled purely from within the cell and do not occur in response to extra-cellular stimuli. But he acknowledges that these famous sea urchin experiments seem to present a challenge for this view. In the experiments, Driesch mechanically separated the cells arising from the first divisions of the fertilized egg and found that the resulting single cells were capable of developing into complete (though unusually small) embryos. And Weismann notes that Driesch takes his experiments to 'fundamentally disprove the existence of special regions in the germ which give rise to special organs' (Driesch 1891; quoted in Weismann 1893, 137). In response, Weismann first makes the following somewhat startling claim: 'It seems to me that careful conclusions, drawn from the general facts of heredity, are far more reliable in this case than are the results of experiments, which, though extremely valuable and worthy of careful consideration, are never perfectly definite and unquestionable' (Weismann 1893, 138).[20] And the 'careful conclusions' to which we must give greater weight than the results of experiments in this case are simply the demands that differential development of the various parts of the organism seem to make for germinal specificity:

> If, however, determinants are contained in the germ-plasm, these can only take part in controlling the formation of the body if, in the course of embryogeny, they reach those particular cells which they have to control, – that is to say, if the differentiation of a cell depends primarily *on itself*, and not on any external factor... We can only thereby arrive at the very simple assumptions, that the primary constituents of the germ-plasm are distributed by means of the processes which can actually be observed in the nuclear divisions, so that they come to be situated in those regions which correspond to the various parts of the body, and that those primary constituents are present in each cell which correspond to the parts arising from it. (Weismann 1893, 138)

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[20] While this may be a surprising methodological injunction, it is perhaps worth recalling that the deterioration of Weismann's eyesight had forced him to abandon his own microscopical research many years earlier (see Coleman 1965, 151).

And although Weismann immediately goes on to acknowledge that reproducing the entire idioplasm in every somatic cell would allow the appropriate germinal material to be available wherever it were needed, he insists that this suggestion is disallowed because it simply forecloses the possibility of *any* conceivable explanation or mechanism of ontogenetic development and differentiation:

> As has just been shown, it is also possible to make the reverse hypothesis, and to suppose that although the whole of the idioplasm is contained in each cell, only that particular primary constituent which properly concerns the cell has any effect upon it. The activity of a primary constituent would thus depend not on the idioplasm of the cell, but on the influences arising from all the cells of the organism as a whole. We should thus have to suppose that each region of the body is controlled by all the other regions, and should therefore practically be brought back to Spencer's conception of the organism as a complex crystal. This simply means giving up the attempt to explain the problem at all, *for we cannot form any conception of such a controlling influence exerted by the whole on the millions of different parts of which it consists*, nor can we bring forward any analogy to support such a view, the acceptance of which would render a great number of observations on the phenomena of heredity totally incomprehensible. (Weismann 1893, 139, my emphasis)

Here Weismann explicitly considers the possibility that the entire germ-plasm is present in the nucleus of every somatic cell and unconditionally rejects it because he cannot conceive of – and indeed judges it impossible to conceive of – any mechanism of ontogenetic differentiation and cellular control that would be consistent with this prospect.[21]

Thus, Weismann's confidence in and insistence on the need for germinal specificity in the face of both the opposing views of his contemporaries and the available experimental evidence rested on a number of distinct failures to conceive of relevant alternative theoretical approaches to particulate heredity. For one, here and throughout Weismann consistently treats the disintegration of the germ-plasm into its diverse constituent elements as the only possible way in which cellular differentiation and ontogenetic development could be directed exclusively from *inside* the cell. But perhaps even more importantly, Weismann supposes that the only potential alternative to such an internal, disintegrative mechanism of cellular differentiation is the possibility (of which 'we cannot form any

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[21] Of course, neither Driesch nor de Vries (nor any other theorist of this period) had actually *proposed* an alternative mechanism of cellular differentiation of the sort whose very possibility Weismann failed to conceive (see below).

conception') that the development of cells is controlled by influences coming from *every* other part of the organism. In this judgment he was surely influenced by the fact that his opponents embraced views which must have appeared to him to have just this character: Driesch, for instance, writes that 'The prospective significance of each blastomere is a function of its position in the whole' (1894, 10; cited and translated in Robinson 1979, 182) and Hertwig that 'all the parts develop in connection with each other, the development of each part always being dependent upon the development of the whole' (1896, 105-106; cited in Robinson 1979, 182).

Nonetheless, this leaves numerous theoretical possibilities unconsidered, including the one that would ultimately prove to be most significant of all for the course of further inquiry: the possibility that the development of various cells containing identical hereditary materials might be differentially affected simply by the varying cues present in their *local* cellular or extra-cellular environments. That is, Weismann seems to have simply failed to consider the possibility (seemingly obvious in retrospect) that the hereditary material is duplicated and passed on intact to each cell in ontogeny and growth, but itself contains or consists of a complex machinery for regulating its own activity in response to different surrounding biological and biochemical conditions. On such a view, different cells could develop quite differently not because different components of the original germ-plasm are present in them, but because different aspects or elements of the identical, complete copies of the original germ-plasm contained in their nuclei are *activated in* or *engaged by* different extra-nuclear and extra-cellular local biological environments. Weismann's insistence that the hereditary material contained in the nucleus *must* be qualitatively different in cells that develop differently forces us to conclude that this alternative possibility simply never occurred to him.[22] Instead, as Churchill notes, 'that Weismann failed to see clearly a fourth option, namely a morphological totipotency of all cells and a physiological feedback mechanism of activation, suggests the limitations imposed on him by the morphological generalities of the age...' (1987, 354n).

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[22] Moreover, Weismann's failure to recognize this possibility is evident at least as early as 1883, when he wrote (while still in the grip of Haeckel's 'overgrowth' conception of reproduction; see Churchill 1968): 'as their development shows, a marked antithesis exists between the substance of the undying reproductive cells and that of the perishable body-cells. We cannot explain this fact except by the supposition that each reproductive cell potentially contains two kinds of substance, which at a variable time after the commencement of embryonic development, separate from one another, and finally produce two sharply contrasted groups of cells' (1883 74).

This is not to suggest, of course, that Weismann would have embraced such a view of ontogenetic differentiation if it had occurred to him. Weismann's famous hostility to the inheritance of acquired characters led him throughout the development of his views in the 1880's and 1890's to consistently oppose the idea that any aspect of the expression of the idioplasm could be influenced by *either* local or global features of the surrounding environment.[23] This presumably would have led him to reject the idea that ontogenetic differentiation might reflect the varying responses of identical copies of the germ-plasm to local variations in extra-nuclear and extra-cellular environments just as firmly as he opposed the idea that it might be achieved by holistic influences from all the parts of the body or all other cells. But the important point for our purposes is that Weismann shows no evidence of having conceived of this possibility in presenting or defending the germ-plasm theory itself: instead he treats the disintegration of the germ-plasm and 'influences arising from all the cells of the organism as a whole' as the only contenders. Indeed, it does not seem unreasonable to suppose that his hostility to the inheritance of acquired characters might have played some important role in preventing him from conceiving of the possibility of ontogenetic differentiation as a response to local environmental variation in the first place.

Of course, while Weismann alone followed Roux in insisting on a qualitative nuclear division and germinal specificity (and these aspects of his account were widely criticized by his contemporaries) he was anything but alone among theorists of the late 19th Century in failing to conceive of this (or any) alternative mechanism of ontogenetic differentiation and cellular control. As Coleman remarks, 'Only nuclear complexity seemed able to account for growth and differentiation, but how it did so was absolutely unknown' (1965, 147; see also Bowler 1989, 84-85). Likewise, Dunn suggests that the problems of hereditary transmission could be solved only 'when some biologists were willing to put aside the intractable problem of development' and that a convincing account of cellular differentiation would remain elusive: the theory of the gene would be accepted after the turn of the century, he argues, 'in spite of the paradox that the mechanism proposed assumed the same variety of units in all cells although the cells themselves became different' rather than because the paradox had somehow been solved or any convincing mechanism

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[23] My thanks to an anonymous referee for *HPLS* for insisting on the importance of this point.

of cellular differentiation with identical nuclear material in each cell had been identified (Dumm 1965, 47-48). In fact, the controversy over this aspect of Weismann's view provides us with at least some evidence in favor of the claim that the alternative he failed to recognize was quite *generally* unconceived, for it is surely reasonable to suppose that one of Weismann's many critics on this score (whether opponents of germinal specificity or proponents of general cellular totipotency) would have been delighted to point out this alternative possibility, *if only such a critic had managed to think of it himself.* Thus our evidence suggests that neither Weismann *nor those contemporaries who made up his scientific community* ever conceived of or considered this alternative mechanism of inheritance and ontogeny, despite the fact that it was equally well-confirmed by the empirical evidence then available and sufficiently serious as to have been accepted by later scientific communities (including our own).

It is worth noting that it is *because* Weismann cannot conceive of any alternative to the disintegration of the germ-plasm into its constituent elements as the mechanism of ontogeny that he is forced to *reserve* copies of an individual organism's germ-plasm for its own germinal cells from the very beginning of its development. That is, because the organism's own idioplasm must be disintegrated over the course of its development and in the process of cellular control, Weismann finds himself forced to account for such phenomena as reproduction by budding (Weismann 1893, Ch. IV) and the formation of germ cells (Weismann 1893, Ch. VI) by assuming that complete copies of the germ-plasm are produced and reserved from the very beginning of its development for this purpose:

> I assume that germ-cells can only be formed in those parts of the body in which germ-plasm is present, and that the latter is derived directly, without undergoing any change, from that which existed in the parental germ-cell. Hence, according to my view, a portion of the germ-plasm contained in the nucleus of the egg-cell must remain unchanged during each ontogeny, and be supplied, as such, to certain series of cells in the developing body. (Weismann 1893, 184)

This 'blastogenic idioplasm' consists of one or more complete copies of the organism's germ-plasm, preserved in a special 'inactive' and 'unalterable' state and passed through particular lineages of cells (the 'germ tracks') in the organism's body, ultimately to be located only in its sex cells (after reduction division) and any other cells in a given organism from which offspring may be generated.

Weismann himself appreciates the close connection between this conviction that a special complete copy of the germ-plasm must be reserved for the reproductive cells from the beginning of ontogeny and his own earlier insistence that it must be by means of disintegration of the germ-plasm that ontogenetic development and differentiation is achieved:

> All these facts support the assumption that somatic idioplasm is never transformed into germ-plasm, and this conclusion forms the basis of the theory of the composition of the germ-plasm as propounded here. It is obvious that its composition out of determinants which gradually split up into smaller and smaller groups in the course of ontogeny, cannot be brought into agreement with the conception of the re-transformation of somatic idioplasm into germ-plasm. If, as we have assumed, each cell in the body only contains *one* determinant, the germ-plasm – which is composed of hundreds of thousands of determinants – could only be produced from somatic idioplasm if cells containing all the different kinds of determinants which are present in the body were to become fused together into *one* cell, their contained idioplasm likewise combining to form *one* nucleus. And, strictly speaking, even this assumption would be by no means sufficient, for it does not account for the architecture of the germ-plasm: the material only would be provided. Such a complex structure can obviously only arise historically. (Weismann 1893, 190-191, original emphasis)

As we have seen, it is because he can conceive of no alternative mechanism of ontogenetic differentiation and/or cellular control that Weismann is forced to insist that the germ-plasm must disintegrate into its constituent elements in the course of its development. And because he judges it impossible that the organism's germ-plasm could be *re-formed* once disintegrated in this way,[24] this in turn leads him to insist that complete copies of the organism's entire germ-plasm must be reserved for and passed along to its reproductive cells from the very beginning of its ontogeny.

Invariance, Multiplication, and the Fate of Active Germ-Plasm

The discussion of the preceding section at least suggests that Weismann also failed to recognize even the possibility of what we might call a *contextual* rather than *invariant* conception of particulate heredity. He does not, that is, seem to recognize the possibility that the activity of the fully developed germ-plasm might depend on the further biological or biochemical context in which it operates.

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[24] The suggestion Weismann is here self-consciously rejecting with this denial is Strasburger's theory of 'germinal return' (see Coleman 1965, 150f).

From our own perspective, this particular failure to conceive of important alternative possibilities is especially surprising in light of the fact that Weismann clearly *does* recognize the potential for interaction *among* the various parts of the inherited germ-plasm. That is, Weismann recognizes that the action of one part of the hereditary material might depend upon what other such materials are also present and therefore insists neither that the development or activation of any particular hereditary germ must invariably produce a particular characteristic in the organism, nor that a copy of a given germ must invariably generate the same trait in a descendent that it did in an ancestor. Instead, although on Weismann's account each id individually contains all the determinants required for the construction and development of a complete organism, any given trait of a particular organism is the outcome of a complex process of competition and interaction among the various constituent elements contained in the many distinct ids making up that organism's idioplasm.[25] Such idioplasm typically includes a large number of homologous determinants (those whose 'function is to control the same part of the body', Weismann 1893, 265), each of which may be homodynamous ('impressing a *like character* on any part of the body'; Weismann 1893, 278, original emphasis) or heterodynamous ('tend to impress a somewhat different character on the same part of the body', Weismann 1893, 265) to one another, and which may also vary in their respective degrees of 'controlling force'.[26] By appealing to a variety of processes of control and competition (including their recombination in sexual reproduction) among such homologous determinants, Weismann is able to offer elegant explanations of any number of observed patterns of individual variation, reversion, the degeneration of characters, the characteristics of interspecific hybrids, changes in the characteristics of a species over the course of its phylogeny, and much else besides. These explanations clearly countenance the possibility that one

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[25] In fact, Weismann would later (1896) develop a much more elaborate theory of the processes of competition, combination, and control between constituent elements of the germ-plasm that determined the course of growth and development (and the changing composition of the idioplasm) in each particular 'track' or intraorganismic lineage of cells.

[26] Although Weismann often writes that each cell is controlled by only a 'single' determinant, other passages suggest that this is meant to imply only that such control is effected simply by a single *kind* of homologous determinant, with competitive and combinatorial propensities (e.g. differing degrees of 'controlling force') among such homologous determinants and their constituent biophors acting to determine the ultimate characteristics of the cell (see Weismann 1893, Ch. 1 Sec. 4 and Ch. IX Sec. 3). Weismann also notes that organismic traits are often determined by the number, arrangement, proportions, repetition, rate of division, or other characteristics of the *various* cells constituting a particular structure, rather than by the ontogenetic fate of any particular cell.

inherited determinant might interact with, interfere with, or otherwise influence the action of another in such a way as to produce variation at the organismic level: 'The power of homodynamous determinants is simply cumulative, whereas dissimilar or heterodynamous determinants may, in the most favourable cases, co-operate to form a single resultant, but may, under certain circumstances, counteract or even neutralise one another' (Weismann 1893, 278).

All this renders it especially noteworthy that Weismann does *not* seem to recognize the possibility that the activity of the germ-plasm (or some particular part thereof) might itself be truly *facultative* or systematically responsive to a range of environmental conditions. That is, while Weismann certainly recognizes that features of the environment can influence what characteristics an organism or cell ultimately comes to exhibit (see, for example, Weismann 1893, 107), he does *not* seem to conceive of the possibility that this might be because the activity of the fully developed germ-plasm *itself* or some group of fully developed hereditary determinants systematically depends on the various cues found in its cellular or extra-cellular environment. This becomes most evident when Weismann considers various ways in which the developmental response of an organism or a constituent cell to its environment *must* itself be facultative, for he can allow for such a response only by *multiplying* the number of physically distinct idioplasms that are potentially available to become activated and guide the development of the organism or cell in question.

In discussing regeneration, for example, Weismann finds himself forced to assume not only that a cell or type of tissue capable of initiating the regeneration of any parts of the organism distinct from itself must contain a special 'accessory idioplasm' ('consisting of the determinants of the parts which can be regenerated by it' (Weismann 1893, 103); as a dedicated adaptation for this purpose, but also that an organism's cells must contain *multiple* distinct accessory idioplasms of this sort if they are to be able to regenerate in multiple directions (Weismann 126-127): he notes that in some segmented worms (such as *Nais* and *Lumbriculus*) an amputated part will not only be replaced in the original organism but will also itself regenerate a complete copy of that original organism, and concludes that every cell capable of such bi-directional regeneration must contain two distinct complements of such accessory idioplasm, each of which is supplied with all and only the supplementary determinants needed to produce the rest of the organism in just one direction or the other. As fresh-water polyps and sea anemones are able to successfully regenerate complete organisms from each part of a *longitudinal* as well as a transverse division, Weismann concludes that the relevant cells of these organisms must each contain *three* distinct accessory idioplasms (one for each spatial direction) again consisting of quite different collections of supplementary ids. In each case, Weismann supposes, the development or activation of just one of these accessory idioplasms is triggered by a 'loss of substance' in the appropriate direction.[27] Thus, Weismann can provide for a facultative response by the *cell* to its environment *only by multiplying the number of different collections of supplementary determinants that might come to control the cell and/or its development*, and not by allowing the response of any given portion of activated idioplasm or of a given collection of developed determinants *itself* to be facultative.

Weismann finds himself similarly forced to multiply the idioplasms that can become activated and take control of the development of a cell in order to account for the various kinds of dimorphism and polymorphism exhibited by organisms. He suggests, for instance, that this must be the case in 'dichogeny ... the form of dimorphism which becomes manifest when a young vegetable tissue, under normal conditions, is capable of developing in different ways according to the external influences to which it is exposed' (e.g. its exposure to light), despite his frank admission that 'I can, however, form no idea as to why such an arrangement is met with in this case' (Weismann 1893, 380-382; see also 111, 114). Organisms experiencing alternation of generations must have '*two kinds of germ-plasm* ... both of which are present in the egg-cell as well as in the bud, though only one of them is active at a time and controls ontogeny, while the other remains inactive' (Weismann 1893, 457, original emphasis; see also Ch. V). And sexual dimorphism also 'must be due to the presence in the idioplasm of *double determinants* for all those cells, groups of cells, and entire organisms which are capable of taking on a male and female form ... One of the determinants then becomes active, its twin half remaining in an inactive condition in the nucleus of a somatic cell, and under certain circumstances becoming active subsequently' (Weismann 460-461, original emphasis; see also Ch. XI). But such doubling of determinants by no means applies only to secondary sexual characteristics: for example, because sex-linked diseases like

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[27] More properly, the loss of substance in one direction simply ends a pre-existing 'resistance to growth' in that direction by the organism's tissues, rather than being a 'stimulus ... in the ordinary sense of the word' (Weismann 1893, 129). Indeed, Weismann appeals to an analogous regenerative process to explain the unwelcome results of Driesch's sea urchin experiments (see Robinson 1979, 181).

hemophilia occur only in members of one sex, Weismann concludes that the cells of the walls of the blood vessels must also have double determinants, with only the 'male' or 'female' determinants becoming active in any given individual. And he takes this in turn to be evidence that '*all, or nearly all, the determinants in the human germ are double*, half being 'male' and half 'female,' so that a determinant for any particular part may cause the development of the male or female type of the corresponding character' (Weismann 1893, 372, original emphasis). He accounts for seasonal dimorphism in a single organism in a parallel fashion, while degrees of polymorphism greater than two require further multiplication of the determinants governing each cell, with Weismann ultimately forced to assume that some kinds of bees and termites have triple and even quadruple determinants in their cells, only one set of which becomes developed or activated in any given individual.[28] Weismann recognizes that he is thus forced to posit an 'ever increasing complexity of the substance which renders repetition of the organism possible,' but insists that 'it is impossible to explain the observed phenomena by means of much simpler assumptions' (Weismann 1893, 468). He seems, that is, to recognize no alternative to *encapsulating* an organism's or cell's developmental response to a particular set of circumstances in a physically distinct accessory germ-plasm which simply takes over and becomes the controlling idioplasm of the cell itself under the appropriate conditions.

This inability to conceive of an idioplasm capable of a facultative response to its environment not only forces Weismann to multiply the physically distinct idioplasms which might come to control a cell under various kinds of circumstances, but also forces him to insist that a substantial *change* in the functioning or operation of a cell must be accompanied by a corresponding *change* in its controlling idioplasm. This feature of Weismann's account becomes especially salient in the course of his discussion of the expulsion of the polar bodies from the egg cell during oogenesis.[29] There he first argues that

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[28] Even when Weismann considers the possibility that polymorphism in bees could be produced by differences in the amount or character of the nutrition with which they are supplied, he conceives of this as a matter of the determinants responsible for particular structures *only becoming active* when supplied with abundant nourishment. Weismann ultimately rejects this particular potential explanation in any case because each of the two forms he is considering has physiological structures that the other lacks (Weismann 1893, 376-377).

[29] According to our own current theory, during meiosis the chromosomes of a single spermatocyte or oocyte are first doubled, producing twice the chromosome number of an ordinary somatic cell. In spermatogenesis, each spermatocyte then divides into four sperm, each with half the number of chromosomes in an ordinary cell. In oogenesis, however, only a single egg is formed

the formation and histological development of the egg cell must be governed by a special kind of dedicated 'oogenetic idioplasm':

> If the nature of the cell is determined at all by its idioplasm, the ovum, while still growing and undergoing histological development, cannot possibly be controlled by the same idioplasm as that which serves for embryonic development. I consequently assumed the existence of an '*oogenetic*' idioplasm in the egg during the period of its histological differentiation, and also that after maturation this substance gives up control of the cell to the germ-plasm.
>
> The question then arises as to what becomes of the oogenetic idioplasm when this change in the control takes place. (Weismann 1893, 349, original emphasis)

Weismann's own earlier answer to this question had been that the oogenetic idioplasm must be *expelled* from the egg-cell to prevent it from interfering with the development of the fertilized egg and that this removal of the oogenetic idioplasm was itself the function of the expulsion of at least one of the polar bodies from the egg during oogenesis. He here allows that new evidence has shown this view of the matter to be mistaken and that the expulsion of the polar bodies does not involve the removal of a special oogenetic idioplasm.[30] But this does not lead him to question the existence of a special oogenetic idioplasm in the first place, and in fact the recognition that no such idioplasm is expelled from the maturing egg cell simply allows Weismann to say with certainty what the fate of this oogenetic idioplasm must be. He continues this section, entitled 'Proof that the Determinants become Disintegrated into Biophors', by concluding that the oogenetic idioplasm must instead be *consumed* in the course of performing its directive function:

> The oogenetic idioplasm must exist, and, using the terminology I have now adopted, it may be spoken of as the oogenetic 'determinant'. This determinant will consequently be the first to become separated from the mass of germ-plasm of the young egg-cell, to disintegrate into its constituent biophors, and to migrate through the nuclear membrane into the cell-body. In this way alone can we account for no trace of it remaining in the nucleus, and for embryonic development not being subsequently impeded by its presence. *This determinant*

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from each oocyte, so this additional chromosomal material must be ejected during the transformation of an oocyte into the egg cell. These packets of surplus genetic material ejected during the maturation of the egg are referred to as the 'polar bodies'.

[30] Perhaps most important in producing this recognition was Hertwig's (1890) careful point-by-point comparison of spermatogenesis and oogenesis, showing that meiosis involves a parallel sequence of unusual nuclear divisions that produces four sperm cells from a single spermatocyte, strongly suggesting in turn that each of the three polar bodies represented an undeveloped egg cell (see Churchill 1968, 106-108; 1970, 433).

> *is used up, and disappears as such;* and the fact that it is not expelled from the egg strongly indicates, if it does not prove, that the control of a cell by a determinant is accompanied by the absorption of the latter.... (Weismann 1893, 350, original emphasis)

Most notable here, of course, is Weismann's insistence that whatever germ-plasm is responsible for the development of the egg cell could not continue to exist in the egg without interfering with the formation of the developing embryo. That is, given that the oogenetic idioplasm is not expelled, it must instead be used up in the course of the formation and development of the egg itself and therefore not remain in the egg when the functioning of the latter radically changes. And Weismann confidently extends the lesson learned in this particular case to the operation of the germ-plasm in general:

> I know of no instance in which there is such a wide difference as regards the activity of the idioplasm in successive cell-generations as is the case in the germ-mother-cells and the mature germ-cells arising from them. If, however, even in this very striking instance of a sudden change of function of the idioplasm, the idioplasm which was active at first is not removed from the cell, such a process cannot occur in any other case; and we are consequently justified in applying to all other cells the conclusion derived from the behavior of the germ-cells, and in considering it as proved that the *active idioplasm of a cell becomes used up in consequence of its activity.* (Weismann 1893, 351, original emphasis)

The most important point here is Weismann's presumption that the germ-plasm or any given portion thereof, once developed or activated, is forced to continuously exert a particular effect on the cell in which it resides until expelled, destroyed, or exhausted. Thus, Weismann's failure to conceive of even the possibility that the germ-plasm might be capable of systematically regulating its own activity in response to the conditions present in its cellular or organismic environment forces him not only to multiply the physically distinct idioplasms that may come to control a cell in order to allow for any facultative response of a cell to its environment, but also to argue that once activated the idioplasm of a cell must be used up (since it is not expelled) in the course of exercising its directive function. That is, these features of Weismann's account and the arguments he makes for them illustrate important respects in which he remains unable to conceive of any contextual alternative to an invariant conception of particulate heredity.

Productive and Expendable Germinal Resources

In the final analysis, however, it seems natural to suggest that the two central failures of theoretical imagination we have seen in Weismann, as well as the further consequences we have noted for his account of inheritance and generation, are themselves rooted in a further and still more fundamental inability to conceive of alternative theoretical possibilities. More specifically, *both* Weismann's failure to conceive of any alternative to disintegration of the idioplasm as the mechanism of ontogenetic differentiation and nuclear control *and* his failure to conceive of any genuinely facultative capacity on the part of the germ-plasm itself suggest in turn that Weismann never conceived of the quite general possibility that the germ-plasm could itself serve as what we might call a *productive* rather than an *expendable* resource for the cell and/or the organism.

That is, Weismann seems to conceive of the germ-plasm as itself necessarily *consisting of* a bundle of material resources to be used in controlling the development and differentiation of cells, and he seems never to consider the possibility that the germ-plasm might instead represent the cell's (or the organism's) own machinery for *generating* or *producing* such materials.[31] Consider, for example, the further inference Weismann draws from establishing to his own satisfaction that nuclear control of the cell must be mediated by the passage of material particles from the nucleus into the surrounding cytoplasm of the cell:

> If then, each vital unit in all organisms, from the lowest to the highest grade, can only arise by division from another like itself, an answer is given to the question with which we started; and we see that the structures of a cell-body, which constitute the specific character of the cell, cannot be produced by the emitted influence of the nuclear substance, nor by its enzymatic action, but can only arise owing to the migration of material particles of the nucleus into the cell-body. *Hence the nuclear matter must be in a sense a storehouse for the various kinds of biphors which enter into the cell-body and are destined to transform it.* Thus the development of the 'undifferentiated' embryonic cell into a nerve-, gland-, or muscle-cell, as the case may be, is determined in each case by the presence of the corresponding biophors in the respective nuclei, and in due time these biophors will pass out of the nuclei into the cell-bodies, and transform them.

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[31] This sense of 'expendable' is actually closest to the original military usage of the term, which designates supplies or equipment that are expected to be used up, destroyed, or sacrificed in the course of a military engagement (e.g. ammunition) and therefore need not be listed on a certificate of expenditure.

> To me this reasoning is so convincing that any difficulties we meet with in the process of determining the nature of the cell hardly come into account. (Weismann 1893, 48-9, original emphasis)

As this image of a nuclear 'storehouse' suggests, Weismann here confidently treats the view that nuclear control of the cell must be mediated by the passage of material particles from the nucleus to the surrounding cytoplasm as tantamount to assuming that the germinal material must *itself consist of* such particles and therefore undergo disintegration and pass out of the nucleus in the course of controlling the cell. He seems never to consider the possibility that the role of the germ-plasm could instead be manufacturing the necessary materials for transmission to the cytoplasm, much less that it could do so in a systematically facultative way; that is, he never considers the possibility that the germ-plasm might represent not the organism's *supply* or *stockpile* (or 'storehouse') of biochemical materials for controlling the functioning and development of particular cells, but instead a sort of biochemical *factory* for producing such materials in response to varying environmental conditions.

It would seem, then, that it is ultimately because Weismann is constrained to think of the germ-plasm as an expendable resource for the cell that he cannot conceive of any alternative to its disintegration as the mechanism of ontogenetic differentiation and cellular control; after all, conceiving of it instead as a productive resource quite naturally suggests that the germ-plasm would generate rather than consist of whatever material particles pass into the surrounding cytoplasm in order to mediate these processes. And as we have seen, it is because Weismann cannot conceive of any alternative to the disintegration of the germ-plasm that he is in turn forced to insist on central doctrines such as germinal specificity and the reservation of the germ-plasm from the beginning of ontogeny. In a similar fashion, it would appear to be because he is constrained to conceive of the germ-plasm as an expendable resource that Weismann fails to conceive of the possibility that the hereditary material might be capable of mounting a truly facultative response to its environment. It is because the germ-plasm simply *consists* of the bundles of material resources it might use to effect differentiation and control that Weismann is forced to regard the activation of one rather than another physically distinct and encapsulated ordered sequence of such resources as the only kind of response to an environment that a cell or nucleus can exhibit. In the grip of this presumption, as we saw, Weismann is forced to provide for systematic variability in the form and function of a cell only by *multiplying* the various expendable idioplasms that might ultimately come to control it and to insist that activated or developed germ-plasm, since it is never expelled from the cell, must instead be *consumed* in the course of exercising its directive function. By contrast, conceiving of the germ-plasm as a productive resource seems to fairly invite the notion that it acts as a persistent physical intermediary between specific conditions in the extracellular or extranuclear environment and the specific directive material responses provided by the nucleus itself.

Conclusion

Perhaps needless to say, we should not be *surprised* that Weismann failed to conceive of all possible accounts of particulate inheritance or even of any particular scientifically serious alternative to his own theory. Not all things are conceptually possible or conceivable at all times, and like all scientists, Weismann worked in a particular historical context with a particular set of assumptions, problems, preconceptions, and fundamental concerns which importantly shaped and constrained the range of conceptual possibilities open to him, in ways that historians of science have made familiar to us. But what goes for Weismann goes equally well for us: the very familiarity of these sources of Weismann's inability to conceive of serious and well-confirmed alternatives to his own theory give us every reason to suppose that we ourselves occupy a similar epistemic situation and that there are well-confirmed and scientifically serious alternatives to our *own* best scientific theories that remain presently unconceived. Thus, the moral is neither that Weismann was unimaginative in failing to conceive of important alternatives to his own view, nor that he was reckless in drawing inferences from what seemed to him in light of the evidence the only forms a successful account of inheritance might take, but rather that even the *best* scientific minds of the past have repeatedly fallen victim to the problem of unconceived alternatives in ways and for reasons that we have every reason to expect apply in the case of contemporary science as well.

Indeed, Weismann's development and defense of his theory of the germ-plasm would seem not only to offer strong support for the challenge I have posed to scientific realism, but also to suggest any number of ways in which we might extend and/or deepen the problem of unconceived alternatives itself. We have noted, for instance, that Weismann's failures to recognize important alternative theoretical possibilities appear to have a nested, hierarchical structure. That is, it would seem to be at least in large part *because* Weismann fails to imagine that the hereditary material might be a productive rather than expendable resource that he fails in turn to conceive of any possible alternative to disintegration of the germ-plasm as a mechanism of ontogenetic differentiation and cellular control or of the possibility that the germ-plasm itself might be capable of a systematically facultative response to its local environment. And these failures of theoretical imagination lead in turn, as we've seen, to Weismann's insistence that a specially inactivated germ-plasm must be reserved for the reproductive system from the beginning of ontogeny, that physically distinct germ-plasms or idioplasms must be multiplied in cells capable of responding facultatively to their environment, and that the idioplasm must itself be consumed (because it is not expelled) in the course of directing the development and activity of the cell. And this nested structure of connected theoretical inferences suggests that the significance of the challenge posed by unconceived alternatives does not ultimately depend (as it might initially have seemed to) on the blanket claim that the theoretical possibilities we regard as neglected were *never* conceived of in *any* way or at *any* time either by a particular scientist or by *any* member of his or her scientific community. That is, even if we were to uncover heretofore unknown evidence that Weismann (or Hertwig, or de Vries, etc.) did in fact catch a momentary glimpse of some of these neglected possibilities through a glass darkly, they do not seem to have been taken into account *when it mattered in this case*, that is, at the time Weismann was willing to draw and trying to justify significant inferences and conclusions about the nature and constitution of the hereditary material, about the proper course of further research, and about what the processes of inheritance and generation must be like. And it is enough to threaten the case for scientific realism if the relevant theoretical alternatives were neither conceived of nor considered when it really counted in this way.

Furthermore, much traditional history of biology regards the latter decades of the 19th Century as a period in which the necessarily speculative excesses of earlier theorists were abandoned and/or replaced by alternatives increasingly grounded in or constrained by the hard empirical facts uncovered by advances in microscopical observation and embryological experimentation. It is well worth noting, then, that Weismann's failures to conceive of important theoretical alternatives well-confirmed by the available evidence undermines at least one related route of response to the problem of unconceived alternatives. It might have seemed natural enough to suggest that unconceived alternatives only represent a serious problem for theoretical science when we are unable to directly observe or detect the central objects of our theorizing. As difficult as it has turned out to be to characterize the relevant notions of direct observation or detection rigorously, it might nonetheless have seemed reasonable to suppose that more-or-less direct observational contact with the entities about which we are theorizing serves to radically constrain the space of serious and well-confirmed theoretical hypotheses in such a way as to eliminate any real danger posed by the problem of unconceived alternatives. But the case of Weismann makes this strategy of response to the problem look extremely unpromising: after all, Weismann was himself among those who knew that they had managed to observe the hereditary material through the microscope and to track its changing character through such crucial processes as cell-division, fertilization, and the formation of gametes, and he made extensive use of the latest observations in nuclear cytology to argue for and against particular claims about the processes of inheritance and generation. Nonetheless, Weismann remained unable to conceive of important theoretical possibilities concerning any number of aspects of this hereditary material, including its constitution, its operation, and its most fundamental character. Thus, even the ability to engage in detailed and systematic observation or detection (in the standard scientific senses of those terms) of the objects of our theorizing seems to offer no proof against the relevance or centrality of the problem of unconceived alternatives.

Nor, it would seem, does the ability to make successful novel predictions in a given domain of theorizing indicate that we are beyond the reach of the problem of unconceived alternatives, despite the currency of this notion in much recent philosophy of science. Weismann's prediction of the need for reduction division in the formation of the sex cells still stands as one of the classic cases of confirmed theoretical prediction in the history of biology, and it was recognized as such even by his contemporaries (see Robinson 1979, 182-183). Nonetheless, Weismann managed to make this surprising novel prediction – about the behavior of a hereditary material that had not yet even been conclusively identified – while failing to conceive of important theoretical alternatives to his own views of the operation, constitution, and fundamental character of that hereditary material itself, indeed the very alternatives that would ultimately be embraced by later scientific communities.

For these reasons I think we must view Weismann's case not simply as supporting, but also as extending and sharpening the challenge to scientific realism posed by the problem of unconceived alternatives. Notwithstanding his successful novel predictions, his systematic and careful observational access to the hereditary material, and the revolutionary advances of his own theoretical insight, Weismann remained unable to conceive of important alternative possibilities equally well-confirmed by the evidence available to him, including the possibility that the hereditary material was a productive resource for the cell, that it could be capable of a systematically facultative response to its local environment, or that there might be *any* mechanism of ontogenetic differentiation and cellular control besides the progressive disintegration of this material. And if I am right to suggest that the historical record has the general character suggested by this single detailed example, then the central challenge to scientific realism may indeed be that posed by the realization that there are probably equally well-confirmed and scientifically serious alternatives to our own theories which nonetheless remain unconceived by scientists of the present day.

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