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Preformation or new formation – or neither or both?

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Preformation and epigenesis have seemed at many times, to many people, to represent clearly distinguishable positions on the issue of how organisms gain differentiated form. Preformationists traditionally have held that the form is already predetermined at the earliest stages of an individual's existence. Epigenesists traditionally have maintained that form emerges only gradually, during the developmental processes. Thus textbooks often refer to *the* preformation–epigenesis debate as if there were only one clear set of differences at issue. Recent historical literature has begun to establish, however, that 'the debate' actually has taken very different forms at different times. Shirley Roe, for example, has convincingly established the way in which the late eighteenth century debate between Albrecht Haller (a preformationist) and Caspar Friedrich Wolff (an epigenesist) took on its particular form because of the philosophical convictions of the participants.[1] 'The' debate then becomes a series of debates with changing emphases and tones as the philosophical and scientific climates changed.

American biologist William Morton Wheeler (1865–1937) recognised the persistence of concern about when form emerges but also some of the changing character of the specific points at issue. He postulated that there exist two different kinds of thinkers at any time. Some are most affected by the 'succession of phenomena, the ceaseless current of events, the changes that alter the complexion of the world, the great qualitative and quantitative differences produced by those changes in that which we call matter.' These observers note the rhythms and focus on the processes of change. Heraclitus, then Aristotle, Wheeler saw as first representatives of this first class of observers. The second class, represented by Parmenides and Plato, notes form instead of process. These latter observers are impressed by 'similarity of the forms and conditions that recur from time to time and from place to place.'[2] Stability, not change, they see when they observe nature. When applied to development, the former represents a physiological and epigenetic view, the latter a morphological or preformationist view, Wheeler held.[3]

Wheeler suggested that these two types of observers constitute stable classes. Yet he also felt that the late nineteenth century had brought new data which required a reworking of the old preformationist–epigenetic distinctions. Thus, though Wheeler did not acknowledge the complexity of the shifts in earlier disputes and regarded the ongoing preformation–epigenesis debate as relatively fixed prior to his own time, he did see major changes by the century's end. Further new perspectives would probably emerge with more data, he felt. Neither a strict preformationist nor a strict epigenetic position would be likely to succeed. Rather:

> The pronounced 'epigenecist' of to-day who postulates little or no predetermination in the germ must gird himself to perform Herculean labors in explaining how the complex heterogeneity of the adult organism can arise from chemical enzymes, while the pronounced 'preformationist' of to-day is bound to elucidate the elaborate morphological structure which he insists must be present in the germ. Both tendencies will find their correctives in investigation.

In fact, as Thomas Hunt Morgan (1866–1945) suggested, by 1901 it made sense to say that 'a process of pure epigenetic development, as generally understood nowadays, may also be predetermined in the egg.'[4]

It is on the changing perspectives of the late nineteenth century that this paper will primarily focus. In particular, I wish to demonstrate the American effort to undercut the German emphasis of the 1890s on distinguishing preformationist and epigenetic positions. Since I will focus on the American work ultimately, I have chosen to outline the German positions which were generally known and of concern to the Americans. Others also played important roles in stimulating American and European discussion, but the ideas outlined here represent the key theoretical positions. August Weismann and Oscar Hertwig represent respectively the revised predeterminist and epigenetic positions which focused on the extent to which form emerges due to inherited or physiological and developmental factors. Alternatively, Wilhelm Roux and Hans Driesch emphasised the extent to which the embryo acts as a self-differentiating mosaic of unstructured material which responds regulatively to external factors. Wilhelm His urged an intermediate position paralleled in significant respects to the American efforts to sort out the extent to which internal and external, inherited and developmental factors direct the emergence of form. The study of sex determination provides an example of one area where the discussion was played out.

The German debates: predeterminism and epigenesis

Before evolution theory, both preformationists and epigenesists addressed the question: when does the embryo come to have the differentiated form that it is supposed to have? Or: at what point does the individual assume the characteristics of its type? Other concerns such as how that differentiation occurs also found expression, but all discussants began with the assumption of conformity to type. After the acceptance of evolution theory, there remained no type to which an individual could conform. Rather, the individual might feel pressures from the environment, hence external influences, as well as the effects of heredity, or strictly internal influences. An individual's form might resemble that of its parents but differ in some ways also. The biologist had to account for development of form with variations from as well as similarities to the parental forms. Since conformity no longer explained form, the embryologist had to provide an account of how that differentiated form appears. Preformation and epigenesis persisted, but with different emphases.

August Weismann (1834–1914) and Oscar Hertwig (1849–1922) served as primary spokesmen for these revised preformationist and epigenetic positions. Though others also contributed to the debates, Weismann and Hertwig provided a comparatively clearcut focus on what they consciously and explicitly regarded as the issues of preformation and epigenesis. They therefore serve to illustrate the state of the discussion in the 1890s. Weismann wrote of development in a number of essays, but his classic *Das Keimplasm* of 1892, translated into English in 1893, provided the focal point for supporters and critics alike.[5] In that work, Weismann explained that he had begun with sympathy toward epigenetic views and had rejected the 'evolutionary' idea that individual form merely unfolds from a pre-existent miniature state in the germ. In particular, Darwin's ideas of pangenesis had caused problems for him initially, Weismann proclaimed, but then he was forced into accepting such an evolutionary or preformationist position himself:

> My doubts as to the validity of Darwin's theory were for a long time not confined to this point alone: the assumption of the existence of *preformed* constituents of all parts of the body seemed to me far too easy a solution of the difficulty, besides entailing an impossibility in the shape of an absolutely inconceivable aggregation of primary constituents. I therefore endeavoured to see if it were not possible to imagine that the germ-plasm, though of complex structure, was not composed of such an immense number of particles, and that its further complication arose subsequently in the course of development. In other words, what I sought was a substance from which the whole organism might arise by *epigenesis*, and not by *evolution*. After repeated attempts in which I more than once imagined myself successful, but all of which broke down when further tested by facts, I finally became convinced that an epigenetic development is an *impossibility*. Moreover, I found an actual *proof of the reality of evolution*, which . . . is so simple that I can scarcely understand how it was possible that it should have escaped my notice so long.[6]

This 'proof' lay largely in explaining, within the context of cell theory, how body parts become so diversely differentiated. Cells become differentiated from each other but also differentiated themselves. This differentiation must result from different kinds of material particles (his biophores), Weismann asserted. This material must allow for transmission of independent structures which are not fixed but subject to variations. Thus '*The independently and hereditarily variable parts of the body therefore serve as an exact measure for determining the number of ultimate particles of which the germ-plasm is composed: the latter must contain at least as great a number as would be arrived at by such a computation*' of the number of variable parts.[7] The variable multicellular organism becomes so complexly differentiated, and thus requires so many different biophores, that even if those biophores were quite small there would not be sufficient space in the germ-plasm for them all. He could not envision a germ which contained a sufficient number of sufficiently variable biophores to explain an organism's situation, so any epigenetic account of development must fail. Instead of to biophores (which would yield varied characteristics by epigenetic development), then, Weismann turned to determinants (or material units which indirectly determine which characteristics will become manifest) as the basic unit of heredity. Some form of predeterminism must prevail.[8]

After making it clear that he held epigenetic views untenable and predeterminism necessary, Weismann then proceeded to detail his theory of the autonomous germ-plasm in heredity, development, and evolution.[9] Briefly, he maintained that 'Ontogeny, or the development of the individual, depends therefore on a series of gradual qualitative changes in the nuclear substance of the egg-cell.'[10] Nuclear changes, presumably with divisions of the chromosomes and accompanying reduction of the chromosome material, act to distribute the determinants for each body feature to different cells. Each cell becomes a particular cell type – such as nerve, muscle, epithelial, or whatever – simply because of the action of the determinants distributed to it.[11] Thus the cells are self-differentiating, 'that is to say, the fate of the cells is determined by forces situated within them, and not by external influences.'[12] It is *not* the case, as some epigenesists would say, that the cell's particular physical location in the embryo determines its fate. It is not the case, for Weismann, that conditions external to the cell itself can direct development.[13] Rather, under normal conditions, each cell has its predestined role because of the inherited determinants and their distribution to different cells during development. Internal factors alone determine development. Ontogeny is not a '"new formation" of multiplicity' or epigenesis, then, but the unfolding of multiplicity, or the evolution of previously invisible multiplicity.[14] There is no simple growth of pre-existing form as earlier preformationists had held. Instead Weismann's view was pre-determinist in a way that emphasised process as well as inherited structure, in that he made some concessions to the gradual manifestation, at least, of form. Determinants hold the key to that 'invisible multiplicity', and the nuclear divisions which distribute determinants to different cells explain development, according to Weismann.

Oscar Hertwig disagreed. Weismann's theory actually abandoned explanation of development, Hertwig felt, and it offered an unpromising closed system. In his classic work of 1894, *Präformation oder Epigenese*, Hertwig focused most directly on Weismann's preformation. In Hertwig's view, influenced by his education under Ernst Haeckel (1834–1919) and his subsequent move to a more direct concern with cytology and embryonic development, Weismann's theory

> merely transfers to an invisible region the solution of a problem that we are trying to solve, at least partially, by investigation of visible characters; and in the invisible region it is impossible to apply the methods of science. So,

by its very nature, it is barren to investigation, as there is no means by which investigation may be put to the proof. In this respect it is like its predecessor, the theory of preformation of the eighteenth century.[15]

Instead of looking to fixed determinants as the source of cellular differentiation, the biologist must look to the complex of external and internal factors which affect cellular development. Instead of holding the developing embryo as a self-differentiating, preprogrammed system, the biologist should regard the embryo as also initially dependent on external conditions, Hertwig urged. Yet Hertwig's views did not represent a simple return to earlier epigenetic positions. He held, in agreement with Weismann, that the germ-plasm is already highly organised at the initial stages of development. From that organised germ, development then proceeds epigenetically to produce differentiated form. Thus, Hertwig believed that his theory should be considered evolutionary but also epigenetic.[16]

For Hertwig, the actions of individual cells and the interactions of cells to form a whole organism remained central. With his eye also on process rather than exclusively on pattern, Hertwig demanded an explanation of such phenomena as cleavage or gastrulation. How could such complex processes, which depend on close cooperation of cells, be explained by Weismann's theory which stressed differentiation and individuation of cells? If the embryo acted as a mosaic with the special determinants distributed to each cell, how could it respond to changing environmental conditions or to experimental conditions, he asked? Gravity, light, temperature, and such factors also manifestly affect development and differentiation, Hertwig felt certain, and Weismann could not explain that fact. Weismann's evolutionary or preformationist theory ignored nature, according to Hertwig, who saw different natural phenomena as demanding explanation.

For Hertwig, the shape of the whole organism and the distribution of materials in the egg played as important a role as the nuclear organisation. While Weismann focused on the nucleus and heredity, Hertwig concentrated on the cytoplasm as well and on development. The internal factors worked with external conditions to effect development. Thus:

I shall explain the gradual, progressive organisation of the whole organism as due to the influences upon each other of these numerous elementary organisms in each stage of the development. I cannot regard the development of any creature as a mosaic work. I hold that all the parts develop in connection with each other, the development of each part always being dependent upon the development of the whole.

Further: '. . . during the course of development, there are forces external to the cells that bid them assume the individual characters appropriate to their individual relations to the whole; the determining forces are not within the cells, as the doctrine of determinants supposes.'[17] Thus Hertwig's views of development clearly differed from Weismann's on at least these points.

It should also be clear that Weismann and Hertwig held different versions of preformationist and epigenetic views than their predecessors had. Though the terms remained, the character of the debate had changed. No longer did the preformationists appeal to the form of the type as already structurally embodied in the germ material and simply growing larger in any literal sense. Weismann's was instead a position of pre-determinism, where material determinants direct the development of differentiated parts. Still an evolution, development involved the self-guided unfolding of pre-determined multiplicity of parts instead of mere growth of preformed parts. The various parts become manifest only gradually as the determinants act in succession; thus Weismann's position moved somewhat toward including epigenesis even while separating heredity and development.[18] Hertwig's epigenesis did still hold form as emerging anew during development. But instead of conforming to type, the emerging organism begins as an organised germ cell, then responds to both internal and external conditions of the whole to grow and develop as a whole organism. The individual cells then work together cooperatively to produce the resulting differentiation. This position thus moved toward embracing some pre-organisation of the egg material. Weismann stressed heredity, Hertwig development, but the distinction was less extreme than in earlier debates.

Two distinct positions thus persisted with Weismann and Hertwig in the late nineteenth century, but they were neither as extreme nor were they as distinctly separated as previous preformationist or epigenetic views. Since each emphasised different problems and made different assumptions, it became unclear what besides rational argument might be considered evidence for one or the other point of view. The introduction of experimental results by Wilhelm Roux (1850–1924), Hans Driesch (1867–1941), and others helped point the way to a redefinition of issues and reorientation of discussion. Still within the general tradition of preformation–epigenesis debates, the exchange between Roux and Driesch exemplified a different emphasis, on the relative roles of internal and external factors in directing development.

An alternative emphasis: self-differentiating mosaic or regulative totipotency?

The 1880s and 1890s brought heated debate about development. Not couched explicitly in earlier terms of preformation and epigenesis, or Weismann's and Hertwig's discussion of determinants and complex whole organisms, instead other contemporaneous debates centred on the extent to which the embryo constitutes a self-differentiating mosaic rather than a regulative body responsive also to changing internal and external conditions. Programmed mosaic or responsive system: which characterises the early embryo? The focus on this revised question represented an emphasis alternative to the more traditional questions about preformation and epigenesis addressed by Weismann and Hertwig.

Wilhelm Roux grappled with the complex problem of development. Eventually he and Weismann came essentially to agree on a theory of distributed determinants as causing development. Yet Roux seemed to the Americans to bring a different emphasis to his work. He elaborated Weismann's basic ideas into his own system of 'Entwickelungsmechanik' (developmental mechanics) and provided experimentally derived support for many of Weismann's claims. In early experiments on orientation of eggs, Roux decided that the orientation did not affect development.[19] As he rotated eggs about an axis, he found no change in development, which proceeded normally in both speed and detail. From this evidence, he concluded that eggs are self-differentiating and do not require external formative influences to guide their way to normal differentiated development.

In his classic, and much-discussed paper of 1888 on half-embryos, Roux set out to test what he saw as the two leading alternative theories of development. As he reported:

> The following investigation represents an effort to solve the problem of self-differentiation – to determine whether, and if so how far, the fertilised egg is able to develop independently as a whole and in its individual parts. Or whether, on the contrary, normal development can take place only through direct formative influences of the environment on the fertilised egg or through the differentiating interactions of the parts of the egg separated from one another by cleavage.[20]

Working with frog's eggs, Roux cited assorted evidence for the self-differentiation of cells. Yet true to his rhetorical pronouncements for 'causal analytical experimental embryology', he maintained that only direct experimentation could establish that development acts as a sum of separate mosaic developments.[21] His experiments in this case consisted of puncturing with a needle one of the two blastomeres after the first cleavage, and a few examples of puncturing one or two of the four blastomeres after the second cleavage. He did not remove the punctured cells, and the early results remained unsatisfying. After modifying his technique, Roux succeeded in obtaining, in about 20% of the operated eggs, the ability of the unpunctured cell to survive and continue developing. These surviving and functioning cases formed his experimental sample, which he examined carefully through traditional histological staining and sectioning techniques.

Roux found a regularity in these abnormal cases. The experimental embryos produced only partial blastula or gastrula stages. The remaining blastomeres did not compensate for the injured blastomeres; rather it seemed that they developed as they normally would. From his results, Roux concluded that 'In general we can infer from these results that each of the two first blastomeres is able to develop independently of the other and therefore does develop independently upon normal circumstances.' Thus, 'All this provides a new confirmation of the insight we had already achieved earlier that developmental processes may not be considered a result of the interaction of all parts, or indeed even of all the nuclear parts of the egg. We have, instead of such differentiating interactions, the self-differentiation of the first blastomeres and of the complex of their derivatives into a definite part of the embryo.'[22] In short, the early developing embryo acts as a mosaic of independent parts. And probably the mosaic is effected by 'qualitative separation of materials', though he acknowledged that proof of that would require further research. From this conclusion of stable developmental pattern followed the suggestion that further study could reveal the exact role played by the particular first blastomeres, a suggestion that the Americans pursued in quite different ways with their cell-lineage work, as discussed later.

Roux did *not* go on in his paper of 1888 to conclude that every step of development produces independently developing cells and hence a perfect mosaic. Though he certainly did not reject such a possibility, he cautioned that 'How far this mosaic formation of at least four pieces is now reworked in the course of further development by unilaterally directed rearrangements of material and by differentiating correlations, and how far the independence of its parts is restricted, must still be determined.'[23] In this work, therefore, he clearly supported the cause of mosaic development, as a Weismannian sort of predeterminism. Yet he did not argue adamantly for an extreme form of predeterminism in which no regulative action could occur. And he left open the possibility that later stages, as the embryo becomes more complex, might exhibit increased dependent differentiation, where cells respond to other cells and to external conditions.

His continued research on half-embryos produced some cases where a whole embryo did result. By that time, though, Roux was sufficiently committed to his mosaic interpretation that he did not question his theory. Instead he generated an auxiliary hypothesis that there exists a reserve idioplasm which is called into action when regeneration or post-generation (following injury) occurs.[24] Despite such modifications, Roux maintained a predeterministic mosaic position. Other studies called Roux's interpretation into question. Of those pointing to contradictory conclusions, the experiments of Hans Driesch received most attention in Germany and the United States. Driesch began, like Roux, with the assumption that embryonic development depended on mechanistic processes and could be explained in mechanistic terms. His experimental results pushed him to different conclusions, however.

In his first of a series of 'Experimental Studies', Driesch followed Roux's lead and tested the potency (or ability to adapt) of cells after the first cleavage stage. Using echinoderm eggs instead of frog's eggs, Driesch expressly sought to repeat Roux's experiments with what he regarded as more durable, available, and easily observed material. Instead of puncturing one of two blastomeres with a needle, Driesch shook the two cells apart, following a technique of Oscar and Richard Hertwig. Apparently Driesch chose a different organism and method because he felt they would offer more easily obtained experimental results, for as Oscar Hertwig had shown, sea urchins presented a particularly favourable embryological subject because of their transparency and resiliency. Experiencing numerous problems with obtaining samples which survived and continued to develop, as Roux also had, Driesch nonetheless generated sufficient cases to discover that they produced half-sized normally structured blastulae. Thus, any theory of predetermination or of the pre-existence of 'organ-forming germ regions' must be wrong. Instead, the cells each retain totipotency, or the ability to adapt to the needs of the organism and become any part, at least until the four-celled stage, Driesch concluded.[25]

In his paper, Driesch did not go further to state that no predetermination occurs or that Roux's theories of cellular self-differentiation or qualitative mosaic division were impossible. He did not endorse such an extreme, definite position at first, but only gradually became convinced of the continued totipotency of cells and hence of the absolutely critical importance of regulation in response to the changing environment during even later stages of development. Continued experiments made him increasingly dogmatic, increasingly anti-mosaic and anti-predeterminism.[26] His work of 1892, with its restrained interpretive comments, served best to underline the central issues in these empirically accessible debates, namely the extent to which development represents an unfolding or self-differentiation according to prescribed pattern or a continued regulated response to conditions.

What had seemed at first a compelling support for Weismann and Roux from Roux's experiments, Driesch undercut with his different results. The question of mosaic predeterminism or regulative epigenetic development remained open. Roux admitted that the mosaic undergoes development and hence is not strictly prestructured, and Driesch recognised that there might be some material arrangement in the germ. The positions were thus less extreme than those of earlier centuries but still clearly distinct, as were those of contemporaries Weismann and Hertwig.

Both Roux and Driesch became increasingly polemical and extreme with further experimental work appearing in print on each side. That tendency to emphasise one position or the other, to support either a preformationist or epigenetic view exclusively, may have stemmed from the researchers' different interests, as Wheeler suggests often happens. Roux, like Weismann, did focus on form, on structure and morphological changes during development. Driesch, like Hertwig, sought instead to understand the processes which take the embryo from one stage to the other. The former looked more to stable, internal factors, the latter more to changing external conditions. The apparent discrepancies of Roux's and Driesch's results received considerable attention from biologists. But the situation was a bit like a Gilbertian comic opera, as Herbert Spencer Jennings later suggested, with all singing 'For you are right and I am right and he is right and all is right.'[27] Historians have perhaps tended to overemphasise Roux's and Driesch's positions and their importance. Roux and Driesch did focus attention on heredity and development, and the apparently contradictory results were important, yet the American biologists at least looked to other alternative accounts of development as well as to elements of both Roux's and Driesch's. What Roux's and Driesch's debate did for the Americans was to underline the need for further evaluation of internal and external influences on development.

A different perspective: Wilhelm His

An alternative to Roux or Driesch, to Weismann or Hertwig, came with the more centrist position put forth by the atypical German anatomist Wilhelm His (1831–1904). He served as an important alternative for the Americans, especially for Charles Otis Whitman (1842–1910), so plays an important part in our story. Though his most well known work appeared earlier (1874), His continued to publish and apparently particularly appealed to some of the Americans because of his cellular point of view and his emphasis on early cellular organisation.[28]

Beginning with the problem of how and when the organism gains its differentiated organisation, His rejected Ernst Haeckel's response, which was becoming a convenient starting point for discussion at the time. Haeckel said organisation came only with the germ layers, with his Gastraea Theory as the most accessible articulation of that view. Haeckel published various works emphasising that the essentially mere vegetative division of cells in early cleavage gives way to the organised gastrula stage.[29] Here, for the first time, the organism has identifiable separate layers which correlate with later parts of the body. For the first time with the gastrula, then, can the organism be considered organised and subject to the adaptive responses through natural selection. Haeckel believed that the earlier stages hold no interest for researchers, serving instead simply to multiply the primary nutritive material. Furthermore, after gastrulation, ontogeny follows phylogenetic patterns of development, or ontogeny recapitulates phylogeny as stated in Haeckel's biogenetic law.[30] Thus, evolutionary history will explain embryonic development, with a few exceptions which Haeckel fitted into a neatly modified version of the biogenetic law.

In contrast to Haeckel, His felt that evolutionary history explained nothing about development. An individual organism does not pass through the stages of ancestral organisms, as Haeckel said. No such primordial ancestor as the Gastraea had ever existed, in fact. Such suggestions add nothing and mislead understanding of developmental processes, which remain essentially physiological processes. Furthermore, His insisted, the earliest cell divisions do not simply separate material in preparation for the all-important gastrular separation into germ layers. The organism is organised from the beginning, he maintained. The fertilised egg has definite organisation, in the form of organ-forming germ regions.

In his most well known work of 1874, His asserted that study of the embryo must begin with the important principle of the organ-forming germ-regions. His convictions expressed in this early work found expression in his later work as well. 'The principle, according to which the germinal disk contains the preformed germs of organs spread out over a flat surface and conversely that every point of the germinal disk is found again in a later organ, I call the Principle of Organ-forming Germ-regions.'[31] In other words, organs exist pre-localised by the time the germinal disk is formed, and each pre-localised germ-region correlates with a later structure, and, indeed, gives rise directly to those later body parts. Developmental differentiation proceeds as the external manifestation of complex, interacting physiological processes internal to the organism. He called for a physiology of development. Look at structure, but also understand the physiological processes which bring about developmental change, His urged.

His's view might seem preformationist. But he denied such an interpretation. Instead, he believed that theories of development fall into four categories rather than the usual two of preformation and epigenesis. His own favourite was neither strictly preformationist nor epigenetic but the rather mysterious 'theory of transmitted movement.'[32] Development of form is the external manifestation of a complex, interacting, lawlike physiological process, His insisted. As with a telegraph message, we cannot see the process but do witness the result. And the message must have had a concrete organised beginning, as development does.[33] It is not the form itself nor the specific building material of the body which begins development, but 'the stimulation of form-producing growth.'[34] Production of form involves both the material medium, or the egg, and the processes of change which are stimulated by fertilisation, according to His.

Notwithstanding His's denials, some did see His as a preformationist. Oscar Hertwig did. In responding to Hertwig in 1901, His reiterated that the attempt to classify researchers into the old two categories of preformation and epigenesis did not make sense any longer. While many found difficulties in explaining the apparently contradictory results of Roux, Driesch, and others, that was partly because of their adherence to such old-fashioned positions, His felt. He found no problem, since he believed that his organ-forming germ regions could explain all. In Driesch's case of the half-sized regular embryos, for example, the separated blastomeres compensate for the missing parts because development involves interactive processes as well as initial organisation. The germ regions are not absolutely predetermined or in any sense preformed, that is, but retain some flexibility to respond to conditions. Form and process work together.[35]

Though Whitman and the other Americans at the Marine Biological Laboratory probably did not read all of His's theoretical work, and though they certainly quoted only very selectively from his writings and avoided some of his more difficult abstractions, they did assume a position similar in some ways to his on the preformation–epigenesis issues.[36] Thus His provided support if not initial inspiration for the Americans. They too held that neither preformation nor epigenesis was adequate in its old form. Nor did the new versions as put forth by Weismann and Hertwig or Roux and Driesch settle for them the issue of how form is achieved. Instead, the question of whether an embryo unfolds or emerges by new formation required a revised approach, they felt. Perhaps organised germ regions and regulative response could together explain development. Supporting this position was the American work on cell-lineage and cytoplasmic localisation that strongly sustained claims for a morphologically differentiated germ.

The Americans: Whitman and the MBL workers

Wheeler's assessment of the situation typified the reaction of those American biologists working at the Marine Biological Laboratory in the 1890s.[37] The M.B.L. offered a unique setting for biologists from various American universities to spend their summers in research, and the work there concentrated in the early years on studies of development, including problems of development, inheritance, and physiology. Epigenetic and preformationist positions admittedly persisted, but neither was any longer regarded as fully in the right. Whitman served as initial spokesman for the preferred intermediate point of view. As first director of the M.B.L. in Woods Hole, Massachusetts, and as head of the important new biology program at the University of Chicago, Whitman exerted considerable influence over the younger group of professional biologists beginning their research careers. In particular, his contribution to the popular series of Friday night lectures at the M.B.L. would have been widely read and discussed.

Whitman had turned to Germany for his training in biology and had continued to read the German biological literature. Exposed while pursuing his doctoral degree in Germany to work in cytology as well as to concentration on phylogeny characteristic of Haeckel and others, Whitman had developed a deep interest in the early stages of development. He was particularly aware of the controversies surrounding the significance of the early stages for later development. The work on cell lineage which Whitman inspired at Woods Hole brought further attention to those early stages. This work also focused interest on questions about the extent to which those early stages exhibited regular, and hence probably inherited, or variable, and hence probably regulated, patterns of cell division. Thus Whitman brought questions about preformation and epigenesis to the attention of American biologists at the Marine Biological Laboratory, and they played a central role in transmitting a controversy active in Germany to an American context.

In his doctoral dissertation work, Whitman considered development of the leech *Clepsine*, exhibiting his conviction that eggs undergo early organisation, and hence some prelocalisation even if not preformation. So, as Whitman concluded, 'In the fecundated egg slumbers potentially the future embryo. While we cannot say that the embryo is predelineated, we can say that it is predetermined.

The "histological sundering" of embryonic elements begins with cleavage, and every step in the process bears a definite and invariable relation to antecedent and subsequent steps....'[38] Bilateral symmetry finds precocious expression in the blastula or gastrula. Whitman considered the various relevant theories and evidence for each, and left many questions open for further discussion – many of which he pursued in a series of papers on *Clepsine*. He operated firmly within the tradition of studies of embryology *and* evolution and certainly did not reject evolutionary concerns.[39] One suggestion which Whitman did follow most closely in those later studies was that of an egg which experiences early organisation.

In another, short, paper of 1878, Whitman pointed out that the traditional view held that a pre-embryonic stage occurs and prepares the egg for its significant cleavage. Growth, impregnation, changes in the nucleus, and formation of the double-walled blastular sac occur during this stage. Then begins serious development with gastrulation, at which point the later stages are more or less sketched out. Only in the previous seven or eight years, Whitman pointed out, had that first pre-embryonic stage begun to receive serious attention. Careful study of the early stages reveals early changes. Yolk-spheres congregate and the nucleus changes, producing an amphiaster which resembles the pattern of iron dust near a magnet. Clearly, with these coordinated nuclear and cytoplasmic changes, 'we have here a life-phenomenon of very great importance.'[40] Other changes also occur in the cytoplasm. The male and female nuclei meet and blend. Complex changes these, presumably holding significance for later development. The early so-called pre-embryonic stage could no longer be ignored, Whitman definitely suggested, though he developed the implications no further in 1878.

By 1887, Whitman had spent two years at Harvard and resided at the Allis Lake Laboratory in Wisconsin. Two papers which appeared in that year demonstrate his growing conviction that the embryo already has some organisation at a very early stage and that researchers should focus attention on the early stages, well before the gastrula appears. In particular, in one paper he asked about the origin and fate of the germ-layers of *Clepsine*, and of the germ bands in particular. How the three germ-layers form and what significance the germ bands, or germ ring, holds remained open questions, which Whitman addressed. Comparing results from different organisms revealed parallels and homologies which went far toward detailing development, Whitman felt. In particular, he found Edmund Beecher Wilson's (1856–1939) studies illuminating. Wilson's *Lumbricus* and his own *Clepsine*, as well as other leeches exhibited a 'complete parallel' in origin and development of the germ bands in particular.[41] In the early cleavages, one finds a forecast of the future organism. Thus,

> Although there is scarcely anything in the external appearance of the eight-cell stage to indicate the relation of its parts to the future embryo, yet we know by what follows that an immense work has already been accomplished. All those fundamental conditions and relations implied in the terms anterior and posterior, right and left, dorsal and ventral, are now definitely established. The ground-plan of the future structure is there, and the segregation and distribution of the building material have advanced far toward completion.[42]

For example, the annelid teloblasts, those particular cleavage products which undergo rapid and frequent division, those 'specialized centres of proliferation', give rise to the germ bands.[43] Clearly some important prelocalisation occurred and a later epigenetic or regulative development could not explain all the phenomena. Whitman sought to investigate these localisations further.

The comparative studies showed that when germ layers cannot be effectively identified and homologies remain unclear, one must look to the 'precise genealogy of the cells', or cell-lineages as such studies were later called. Germ-layers may not always give rise neatly to the same adult parts, and thus the phylogenetic relations cannot be discovered in the germ-layers. The germ-layer theory which finds organisation as beginning only with the germ-layers thus causes problems. 'When, as in the case under consideration, we find an organ arising sometimes from the ectoderm, and at other times from the mesoderm, we have to admit that there is no fixed and impassible boundary line between these two layers; and that its association with this or that germ-layer is not an infallible guide to its morphological identity.'[44] Look, then, to cell lineages, to the way in which particular cells correspond to particular parts of the germ-layers. Only then will you be able to sort out difficult questions of which parts are homologous to which, and which thus share ancestral, evolutionary relationships. Traditional concern with evolution and homologies of germ layers continued in Whitman's work, but the focus had begun to shift to earlier, cellular changes.

A second paper of 1887 underlines this new focus. Examining maturation, or preparation of the egg to receive the 'spermatic element', and fecundation, or 'those attending changes in the protoplasm which form the concluding steps in the premorphological organization of the egg', Whitman admitted that the majority had come to regard the nucleus as the 'primum mobile' of development.[45] The movement of the two pronuclei was widely regarded as evidence that the nucleus controls developmental changes. But no, said Whitman. The pronuclei move through the cytoplasm. Indeed cytoplasmic forces direct the nuclear movements, as seen with the formation of astral lines through the cytoplasm. The egg cytoplasm exerts just as much influence as the nucleus, even at these earliest stages. Cytokinesis (movement of the cytoplasm) and kinokinesis (movement of the nucleus) work together, cooperatively.

With this study, Whitman had embarked on a series of efforts pursued over the next several years to establish definitely not only that the embryo undergoes early organisation, hence that it is pre-organised, but also that cytoplasm exerts influence as well as the nucleus, hence that no complete nuclear determinism occurs. This work brought him directly into the revived debates over preformation and epigenesis as well as disputes over the significance of the cell theory.

Whitman rejected all the extreme positions. Those who argued for either preformation or epigenesis alone missed part of the story, he felt. Instead, 'The truth appears to me to lie on both sides, the error consisting only in unduly exaggerating the relative importance of one or the other factor'. Clearly nuclear changes occur, and they seem to play a role in directing cellular development at least. But the nucleus likely has arisen only by secondary adaptations and cannot be the 'seat of formative and regenerative energies.'[46] In some cases the cytoplasm directs the nucleus, as in the case of fertilisation which he had discussed the year before.[47] So both the nucleus and the cytoplasm exercise some directive control. But not all. The organism as a whole also exhibits a physiological unity, it responds with regulative reactions to changing conditions. A full explanation might require a move beyond such mechanistic accounts as biology traditionally uses. Perhaps new forces enter the process of development. Thus, none of either the preformationist or the epigenetic theories could offer a full account of development, Whitman insisted by 1888. Further study of development and the relative importance of predeterministic and epigenetic regulative factors remained an important problem for biologists.

In two lectures at the M.B.L. in 1894, Whitman returned to the debates. His comments especially in the 'Prefatory Note' indicate his disagreement with the current of opinion. In particular, the apparently contradictory experimental results of Roux and Hans Driesch echoed by experiments from some of the M.B.L. crowd, probably stimulated Whitman's concern. Roux's mechanism and Driesch's both seemed exaggerated and mistaken. Claiming that he had no particular view of his own to defend, Whitman concluded that he sought instead 'to have well-defined standpoints and clear ideas of guiding principles.'[48] Recognition of the initial orientation of cytoplasm and the whole organism, would bring the drift of opinion toward a new standpoint, more akin to His's emphasis on compromise and new definitions. Instead of the old extreme positions which sought to explain development as *all* due to preformation or *all* due to epigenetic responses, ask a new question: 'How far is post-formation to be explained as a result of pre-formation, and how far as the result of external influences?' In other words, what are the relative contributions of internal and external factors in directing development? As Whitman concluded, agreeing with a contemporary, 'This statement compasses the whole situation: "the successive formation of parts not previously existent", represents the accepted verdict on the old issues and the expressions, "imposition from without", and "generation from within" define the new issue, which lies wholly this side of the old . . . .'[49]

In a lecture of 1894, Whitman explicitly addressed the preformation–epigenesis debates. Effectively, he argued that anyone espousing solely one side or the other exhibited arrogance, for these two views remained complementary. Each had components of both truth and error.[50] What biology needed, he urged, was a clear formulation of the relevant standpoints and then investigation to discover the relative validity of each. Biology was actually ready to move to a new standpoint, once the issues became clarified. Instead of argument about whether development occurs by preformation or post-formation, then, the modern biologist should explore how far post-formation, or differentiation during later developmental stages, can be explained by the existence of preformation, or early organisation of the egg. How much depends on the developmental response to external conditions rather than on programmed internal unfolding?[51] This new question comprised such a very different problem than the old dispute, Whitman felt, that to an old preformationist, someone like Weismann would appear as an epigenesist since his system included some new generation during development of parts which had not previously existed preformed. Instead of on preformation or epigenesis, Whitman clarified, the new issue centred primarily on whether generation occurs from within or is imposed from outside.[52] And surely, the prudent biologist must acknowledge that some of both internal and external influences act together and should set out to study their relative importance and the way in which the two sets of factors work together.

Whitman did not believe that pre-organisation explained everything; for example, cleavage planes were not pre-set. Whitman rejected as inadequate any sort of developmental mechanics which sought to explain development while ignoring the initial historically derived organisation of the egg. He took a moderate position instead: some germinal organisation occurs, but later processes in response to conditions also play a role. Evolution and epigenesis, but neither in the old form.

In succeeding essays, Whitman pursued the same themes and developed one of his favourite prescriptions for American biology: cooperate! Biologists should cooperate among themselves, they should use a variety of methods where more than one could prove productive, and they should explore a variety of standpoints on a problem. Do not choose one over-arching theoretical framework to guide your work, he urged the young biologists. Do not become set in your ways or in your ideas. Consider alternatives, avoid buying into dogmatic statements of extreme positions.[53] For example, move beyond preformation–epigenesis debates to new understanding of heredity and development.

At least some of the young biologists at the M.B.L. agreed with much of Whitman's view at first. Beginning with work on cell lineage, they settled to work to ascertain the extent to which the egg is initially organised. Their study of the earliest developmental stages, which carefully traced the origin and fate of each cell through the early cleavage stages, received inspiration from His (and others) by way of Whitman.[54] This concern with tracing cell fates might suggest a strong preformationist position, but that concern was moderated by a conviction that regulation also occurs. Regeneration and transplantation studies argued for regulation rather than mechanistic determinism. And work by Jacques Loeb (1859–1924), for example, suggested that external conditions and accidents such as

where the cleavage planes occur exert more important influences than a preformationist position would allow. Thus, Wheeler for example, recognised the old preformation–epigenesis distinction as no longer useful and acknowledged that only further research would advance understanding. And researchers such as E. B. Wilson and Edwin Grant Conklin (1863–1952) took up cell-lineage studies and addressed the preformation–epigenesis issues. They also began with the conviction that the previous statements of the distinctions no longer proved useful. But each went on to draw his own distinction.

Variations on a theme: Wilson and Conklin

Wilson agreed with Whitman that neither the old preformationist nor the old epigenetic position made sense any longer. After completing his own study of the marine worm *Nereis*, he concluded that the egg definitely exhibits some early organisation. In his major text of 1896, *The Cell in Development and Inheritance*, Wilson emphasised that biologists still had no account for the orderly progression of development. Both Weismann and Roux, on the one hand, and Hertwig, on the other hand, demanded too many assumptions and explained too little. 'The truth is', Wilson concluded, 'that an explanation of development is at present beyond our reach. The controversy between preformation and epigenesis has now arrived at a stage where it has little meaning apart from the general problem of physical causality.'[55] Clearly, part of the germ is inherited. Presumably it reflects the conditions acting on the germ material in earlier generations, which suggests a form of evolution or preformation. Yet, against that is the power of regeneration, which suggests at least some ability of new formation, or epigenesis. Much remains to be explored, Wilson concluded in 1896.[56]

In 1905, Wilson again addressed explicitly the issue of preformation and epigenesis. Over the intervening decade, his researches had led him to more certain convictions about the nature of the inherited germ at least.[57] Yet he continued to maintain that some elements of what had been considered preformation and epigenesis both played roles in explaining development.

Alice Levine Baxter has considered Wilson's work of that period and has concluded that Wilson 'was more of a preformationist than an epigenesist', yet 'that his definition of the term "epigenesis" was rather narrow', and that his particular views of preformation in fact helped Wilson to accept the chromosome theory which caused problems for some of his contemporaries such as Thomas Hunt Morgan (1866–1945).[58] Baxter's very useful studies of Wilson do show him as one of those Wheeler would have identified with morphology and with explaining changes in form rather than in processes of change. Baxter is convincing in establishing the importance which Wilson assigned to chromosomes. Wilson's concern with inheritance *and* development found focus in a nucleus of inherited chromosomes which he saw as programmed in some way to direct development. Yet it is perhaps misleading to label Wilson as a preformationist at all. Really he embraced some elements of both – while rejecting both in their previous or more extreme senses. The important point remains that Wilson saw the debates over development as having changed, away from the traditional arena in which preformation–epigenesis debates took place. Instead of concentrating on determinants or the complex functioning whole organism, self-differentiation or regulation, intrinsic or extrinsic factors, per se, Wilson returned to the traditional developmental question about how production of form occurs, by unfolding or new generation. He then set out his new response.

For Wilson, 'whether the embryo exists preformed or predelineated in the egg from the beginning or whether it is formed anew, step by step, in each generation': that was the traditional form of the basic question of preformation and epigenesis.[59] Recent research showed that in at least some organisms the early cells are directly and regularly correlated with parts of the future body. Other cases do not exhibit such regularity. No paradox here, Wilson said. The existence of 'organ-forming stuffs', some of which are actually visible as differentiated regions of the egg, could explain both phenomena. 'The evidence is steadily increasing', he wrote,

> that such stuffs exist, that they have a definite arrangement in the egg, and that in cases where the form of cleavage is constant they are distributed in a definite way to the cells into which the egg splits up. The cleavage-mosaic is accordingly to be conceived as an actual mosaic of different materials that are somehow causally connected with the development of particular parts.[60]

Thus, for Wilson, to the extent that such material stuffs exist and are distributed in a regular, definite way correlated with late development, to that extent only can the origin of differentiated form be regarded as mechanical and as due to prelocalisation. But that extent may not, in fact, extend far. The prelocalisation may remain only very general, with the majority of details of differentiation coming from non-prelocalised factors.

Confirming such a conclusion, other studies showed that only a few stuffs exist in the early stages 'and that as development goes forward new stuffs are progressively formed and distributed.'[61] To this extent, the actual progress of development is epigenetic and not evolutionary. The embryo emerges only gradually. Yet differentiation is guided by causes lying deep in the hereditary material, presumably in the chromosomes, though the chromosomal role remained not completely demonstrated. This nuclear chromatin does, therefore, control development and offers a sort of preformation, but development remains truly epigenetic in essence.[62]

Whether Wilson was really more a preformationist thus loses importance here. Much more significant is the clear way in which he set up the discussion in 1905. Both preformation and epigenesis operate, yet it nonetheless made sense to separate the two, and to discuss each separately. Moving away from His's and Whitman's concern with uncovering the way in which internal and external factors inevitably work together, Wilson at least rhetorically separated what he saw as the components of preformationist and epigenetic development. Preformation he regarded as linked with inheritance and with chromosomes. Epigenesis he linked with developmental processes and with the cytoplasm and the organism as a whole. Though still regarding problems of heredity and development as essentially related, and though continuing to consider both together, as in his revised *The Cell*, Wilson's discussion of the two made clear that two separable factors operated to guide development. A logical conclusion followed that researchers could address each separately. Wilson himself pursued a path deeper into the inherited material of the nucleus, into the chromosomes and their complex dances during cell division. This particular separation became increasingly important throughout the twentieth century as study of heredity became genetics, of development became embryology, and the two increasingly diverged. A logical and perhaps expedient divergence, given assumptions at the time, but one which brought loss as well as gain.[63]

Wilson's fellow cell-lineagist, Conklin, also began with Whitman's concern for revising the preformation–epigenesis issues. Conklin, however, disagreed with Wilson's increased emphasis on the nucleus as primary bearer of inherited determinants for development. Nuclear divisions could not explain differentiation.[64] An ardent 'friend of the egg', Conklin urged instead the central importance of cytoplasmic factors. The egg is organised early, he agreed with Whitman and Wilson. Yet rather than turning to the 'deep hereditary stuffs' in the nucleus and chromosomes to explain that phenomenon, he urged, let us examine the cytoplasm itself and identify relations between early differentiated organised areas and parts of the later embryo. Agreeing with Wilson's general view that some sort of formative material represents the beginning of differentiation, Conklin continued to call for a different emphasis, which kept heredity and development together by examining the relations of inherited stuffs and later development. In a later paper, he neatly summarised his continued convictions:

> What is the formative agent in embryonic differentiation? ... It is impossible to understand, i.e., to make intelligible, development except as a result of the formation and localization of different material substances. Indeed development consists in morphological division of substances and physiological division of labor. Cytologists and geneticists have made notable advances in the study of the distributions of differentiated chromosomes and genes in the germ-cells, but the cytoplasm of the egg cell has frequently been regarded as mere foodstuff for these nuclear elements, in spite of the fact that practically all differentiation takes place in the cytoplasm. We are beginning to realize that the central problem of development lies in this relation between the genes and the cytoplasm, and that the cytoplasm is something more than mere nutritive 'stuff'.[65]

For Conklin, one particularly accessible problem for development lay with ascertaining the extent to which and the way in which early cleavages of the egg correspond to later embryonic development. Does the division of cells play a causal role in producing differentiated form? Three possibilities exist, he reported. Either (1) cleavage planes separate already differentiated germ regions, (2) cleavage planes cut randomly across germ regions, or (3) cleavage planes cut through undifferentiated, homogeneous material and do not yield differentiation.[66] Roux's mosaic theory represents the first. Driesch's views represent the third. And such views as Whitman's hold the middle position, Conklin felt. Like Whitman, Conklin sought a compromise, but in a different way. Each of the three alternatives for cleavage holds true for some cases, he concluded. Some organisms exhibit relatively more, others relatively less determinate cleavage. Determinate cleavage holds when the cleavage pattern is constant and differential (regularly correlated with later differentiated parts).

Indeterminate cleavage is neither. Determinate cleavage occurs because of protoplasmic direction, while indeterminate cleavage responds more to extrinsic environmental factors.[67] No nuclear determinants or even deep nuclear directives for Conklin. The active, responsive and initially inherited cytoplasm holds the key to explaining development.

Though Conklin did not go on explicitly in 1905 to tie his analysis with preformation–epigenesis discussions in any detail, he was certainly aware of such discussions. Given the context of his other work and of his contacts at Woods Hole, it is fair to assume that he regarded his determinate–indeterminate cleavage distinction as addressing the same problems. Determinate cleavage represents something like preformation, in an organism which acts like a developmental mosaic. Indeterminate cleavage represents epigenesis, or a responsive organism. Both occur, in different measures in different organisms. For Conklin, further consideration of the issue would have to address the extent to which and way in which the separation of blastomeres correlated with organised germ regions as well as with later-differentiated parts. Mapping such relations could go far to demonstrate how form becomes differentiated and when, he felt. Conklin denied the distinction of heredity and developmental processes, which formed part of Wilson's working assumptions after 1905 and 1906. For Conklin, heredity and development remain inextricably connected.

In his Harris lectures of 1914, Conklin addressed preformation and epigenesis directly. Yet neither in the 1915 nor even by the 1930 edition did he mention the nucleus or chromosomes in his discussion. Modern studies recognise that neither the old preformationist nor epigenetic positions hold true, he summarised. Rather, the germ has organisation, and development brings a formation of 'new materials and qualities, of new structure and functions.'[68] Still emphasising both internal and external conditions as shaping development, and still ignoring the separation of heredity and development, Conklin concluded that

> Increasing complexity, which is the essence of development, is caused by the combination and interaction of germinal substances under the influence of the environment. The organization of the oosperm may be compared to the arrangement of tubes and flasks in a complicated chemical operation; they stand in a definite relation to one another and each contains specific substances. The final result of the operation depends not merely upon the

substances used, not merely upon the way in which the apparatus is set up, but upon both of these things, as well as upon the environmental conditions represented by temperature, pressure, moisture or other extrinsic factors.[69]

While researchers such as Whitman, Wilson, Conklin, and Wheeler pursued their particular pieces of the middle ground between pure determinism and pure regulation, there were others who took positions a bit closer to Driesch's regulative perspective than any of these more morphological researchers. Those of Wheeler's investigators inclined toward process, those physiologists, stressed external factors and indeterminate early cell divisions more strongly. Men such as Morgan, Jacques Loeb (1859–1924), Charles Manning Child (1869–1954), or Frank Lillie (1870–1947) emphasised responses to changing conditions as causes of differentiation. These men remained adamant epigenesists in that they believed that form emerges only gradually, only as the result of regulative responses to external conditions. Not accidently did both Morgan and Loeb undertake extensive studies of regeneration, where regulation remains most obviously at work. Nor was it accidental that both Morgan and Lillie became major participants in the discussions of sex differentiation and sex production. The question of when and how an individual comes to have one sex or the other became something of a micro focus for the macro concern over whether development as a whole results from preformation or a new formation.

The focus on sex: heredity and developmental, predeterminism and epigenetics

Sex offers a relatively clear case for study of the roles of heredity and development, an inherently interesting case, and after 1902 an apparently accessible case for study. During 1905–10, debates over sex determination became increasingly central to discussions over the relative role of heredity and development, or predeterminism and epigenesis. Partly this occurred because an individual becomes either one or the other sex, rather than some intermediate, and the researcher can tell relatively easily which sex has been developed – unlike the case with many other characteristics. Ultimately, it was sex determination which led Wilson further into the nucleus, pushed Morgan to genetics, and illustrated the separability of the related problems of sex inheritance and sex development or production.

Complex problems sorted out for sex determination pointed the way to understanding more general problems of heredity and development. In fact, sex differentiation promised a productive research program, with a viable framework to advance the process of clarifying previously confused issues. This study was thus central to changing attitudes about preformation and epigenesis, about heredity and development, or genetics and embryology.

In 1891 Henking discovered the regular existence of an unusual body in the nucleus of insects. Further work by 1902 identified that body as indeed a nuclear chromosome. The American, Clarence McClung (1870–1946) termed it an accessory chromosome and suggested that presence of the accessory determined maleness.[70] He was wrong, in fact, since the accessory actually determines femaleness in his particular insect species. Yet his suggestion that there exist two different types of spermatozoa, distinguished by their chromosomes, and two resulting different types of fertilised eggs, focused active attention on sex determination. If sex is determined by a chromosome, it seemed, then a sort of predetermination occurs, but perhaps the chromosome and sex were connected only secondarily, not causally connected. Did the apparently inherited chromosome determine, direct, or only follow sex determination, was the question.

For over a decade, numerous researchers had argued about whether sex differentiation in particular is predetermined in the fertilised egg, due to factors internal to the organism, or whether it emerges only gradually, guided instead by regulated response to external factors. Temperature, food, light – such factors might possibly determine each individual's sex, and to many physiologically oriented researchers prior to 1910, such factors did seem to be decisive.[71] By 1903, the internalists had won.[72] But the internalist position had fragmented, forming a range of opinions with two reasonably defined views on either end of a spectrum. Internal inherited factors determine development, said one group. The other group insisted that internal physiological responses and definitely not inheritance direct development and differentiation. The disputes centred on the significance for development of those accessory chromosomes in the nucleus which Henking and McClung had identified. Whether development occurs by preformation or epigenesis had become largely an issue over inheritance of chromosomes *vs.* regulative physiological development.

By 1905 Americans had assumed the primary roles in debating the case of sex determination, with considerable input also offered in particular by German cytologist Theodore Boveri (1862–1915). Though many people took part, the chief advocates of nuclear inheritance for purposes of this discussion included Nettie Stevens (1861–1912) and Wilson.[73] Against the ability of nuclear inheritance to explain the significant facts of development sat Morgan, Conklin, and Lillie, along with Loeb and Child. Sex chromosomes *vs.* interactive gradients and complex hormonal activity as *the* primary factor determining sex: we all know which position gained at least apparent dominance.[74]

This is not the place to expand on details of the debates, but the central point is clear and directly relevant. Some researchers willingly saw the regularity of chromosome divisions as evidence for chromosomal significance in development. Rather than concluding only what that evidence showed, however, namely that some correlation occurred, some went on to claim that chromosomes actually cause differentiated development. Though cautiously stated, this is the clear implication of Wilson's work after 1905, and of *Drosophila* studies by the Morgan group after 1910. Weismann and Roux had already presented logical arguments for a system in which determinants actually direct a mechanical, pre-programmed succession of developmental events. Though the evidence accumulating to show a correlation of chromosomes and characteristics such as sex was not conclusive, it did tend to push researchers in the direction of such neat mechanical systems as Weismann's and Roux's. Even previous sceptics of any such deterministic system, such as Morgan, became converts not only to the idea of chromosomal significance but even to a stronger hereditarian position, whereby heredity serves as the starting point and later determinant to development. The ability of a hereditarian chromosomal theory to address a variety of phenomena made such theories attractive to many including Morgan. Furthermore, such broad suggestive theories could serve as foundations for productive research programs.[75]

In contrast, other researchers reacted vehemently against such hereditarian views, paralleling with greater force Conklin's response to Wilson's stress on the nucleus. Some remained hereditarian but stressed the organised cytoplasm as inherited. Development can never be explained by the action of inherited materials, they argued. The organism represents a dynamic, ever-changing whole which

responds to constant alterations in conditions both inside and outside the organism. Although the egg is manifestly inherited and although it may already possess some pre-organisation at the earliest stages, it is physiological regulation, the actions of hormones and enzymes and chemicals which ultimately direct development. Inherited chromosomes really explain nothing of development. Response of the organism is key.

By 1910 these commitments had become embodied in divergent research programs. Genetics and embryology emerged as relatively defined research directions. Though biologists still accepted that both heredity and development occur, they moved away from the earlier versions of an intermediate position after 1910. Whitman's urge for cooperation and inclusion of both heredity and development did remain in the background. Biologists understood that something was inherited and also that actual differentiation was produced only gradually. But effecting a research program to deal productively with both proved difficult. Conklin tried, as did a few others such as Richard Goldschmidt (1878–1958). But attention focused instead on the relatively quick results of Morgan's genetics of sex heredity or on physiological hormone studies of sex production. Biologists had moved beyond a central position in their search for productive results through divergent research programs.

Epilogue

Even today researchers have followed divergent, specialised paths. Biologists have largely ignored the various urgings by His, Whitman, and Conklin that differentiation represents an interaction of both intrinsic (hereditary) and extrinsic (developmental) factors. The study of heredity, largely through genetics but also to some extent through study of cytoplasmic inheritance, has taken research in a different direction from embryological research on development. A fairly typical modern view, as stated by the Medawars, though ignoring cytoplasmic inheritance, holds that 'Genetics deals with the characters of the information transmitted from generation to generation, "epigenetics" (Waddington's term) deals with the processes by which this information is translated into real life – into flesh and blood and distinctive behavioural characteristics.' Thus, '. . . there *is* some real meaning in the antithesis: the genetic instructions according to which development proceeds are indeed preformed, but their realization is *epigenetic*, i.e. turns upon influences acting upon the embryonic cell from the outside. . . .'[76] Though biologists today generally acknowledge with the Medawars that both heredity and development occur, most proceed with their research as if only one or the other really mattered for explaining development, while the other provides only background.

Why? Why did the search for compromise by the Americans in the 1890s, which seemed so sensible and obvious, give way to this new division? Does the answer lie with the living processes themselves, with the way biologists think, or with external demands and constraints on science? Can biologists move forward successfully to a satisfactory understanding of both inheritance and development, or ought they even to try? These complex questions cannot be answered easily, and here I can offer only suggestions.

The answer does not, I feel certain, lie in the organisms themselves. Life does not involve a period of heredity neatly separated from a period of development. The egg manifestly develops even before fertilisation, while inherited material obviously continues to exert effects long after. Heredity and development are much more intricately interconnected than most research programs in either genetics or embryology after 1910 have admitted.

The willingness to divide complex biological processes into categories comes from the biologists themselves, then, and their responses to external demands placed on them. By 1910 a fairly well defined sense existed of what constituted a productive research program in biology. Answerable questions, definitive results. Not grand umbrella theories which proposed to explain everything at once. Not descriptive tidbits about pieces of development. Instead, biologists sought to formulate questions which were addressable through observation and experiment, thus yielding positive results. How best to conduct productive research? Narrow the problems and tackle accessible questions with available materials. Thus division of larger problems into questions of heredity and of development resulted – and has persisted.

Undoubtedly, Wheeler is also correct in claiming that different kinds of people exist and work with different assumptions. Perhaps some do find stable patterns more accessible and more comforting and hence find genes, prelocalised cytoplasm, and hereditarian assumptions most acceptable. Perhaps others find changing patterns and the processes of differentiation more intriguing problems and

find developmental approaches more acceptable than hereditarian assumptions. More probably, there are more than Wheeler's two clearly distinct kinds of thinkers. Biologists probably fill a range of different convictions, with some falling between the extremes.

That middle ground receives less attention for a variety of reasons. It has traditionally promised less than extreme positions in the way of those definite and exciting results that granting agencies and administrators like. A struggle for authority for research funds and jobs in a world of increasing specialisation may also foster or at least reinforce a division of labour.[77] As a result researchers have felt pressures to concentrate in order to realise results, and they have accepted the expediency of rhetorical emphasis on one factor to the exclusion of others. Thus what biologists study in the laboratory may obscure their more complex, but less accessible convictions about the way form emerges.

I have traced the transformation and fall of a dichotomy in late nineteenth century biology. The debates between Weismann and Hertwig bore a family resemblance but were not precisely identical either to their eighteenth century predecessors or to the later exchanges. In America the dichotomy of preformation and epigenesis itself was rejected, only to be revived in a different form in the alternative focuses of research in genetics and embryology. Functionally, at least, biologists have since 1910 operated as if heredity and development could be neatly separated. Presumably, however, the process of transformation is never over, and the distinctions of current practice will themselves move into the historical background.

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23. Roux, 1888, p. 28.
24. Further consideration of Roux's theories here would carry the discussion too far afield. See Churchill, *Wilhelm Roux*, for further discussion.
25. Hans Driesch, Entwicklungsmechanische Studien. I Der Werth der beiden ersten Erzeugung von Theil- und Doppelbildungen, *Zeitschrift für wissenschaftliche Zoologie* (1892) 53, 160–78. Also in Willier and Oppenheimer, pp. 38–50. The page numbers cited here refer to the more accessible translation.
26. For example, he had begun to shift by 1894. See Driesch, *Analytische Theorie der organischen Entwicklung* (Leipzig: Wilhelm Engelmann, 1894).
27. Herbert Spencer Jennings, Biology and Experimentation, *Science* (1926) **64**, 97–105; citation p. 99.
28. Though the Americans' awareness of His has been acknowledged by some, the importance of that connection has not generally been appreciated. In particular, the tradition of concern for cell development, embracing the work of Schwann and Schleiden, Remak, and Virchow, had an important impact on His. As demonstrated by their citations and the problems they considered important, it is clear that Whitman and Wilson also were influenced by that tradition. Thus His's influence on American biology calls for further examination.
29. Ernst Haeckel, *Monographie der Kalkschwämme* (Georg Reimer: Berlin, 1872);
Gastraea-Theorie, *Jenaische Zeitschrift* (1874) **8**, 1–55;
Die Gastrula und die Eifurchung der Thiere, *Jenaische Zeitschrift* (1875) **9**, 402–508;
On Haeckel and germ layers, see: E. S. Russell, *Form and Function* (London: John Murray, 1916), chapter 16;
Alice Baxter, E. B. Wilson's 'Destruction' of the Germ-Layer Theory, *Isis* (1977) **68**, 363–74; especially pp. 362–6;
Jane Oppenheimer, The Non-Specificity of the Germ-Layers, in *Essays in the History of Embryology and Biology* (Cambridge, Massachusetts: MIT Press, 1967), pp. 256–94.
30. Jane Maienschein, Cell Lineage, Ancestral Reminiscence, and the Biogenetic Law, *Journal of the History of Biology* (1978) **11**, 129–58.
31. Wilhelm His, *Unsere Körperform und Das Physiologische Problem ihrer Entstehung* (Leipzig: F. C. W. Vogel, 1874), p. 19, E. G. Conklin translated this passage, 'Cleavage and Differentiation,' *Biological Lectures* (1898) 1896–7: 17–43; citation 18–19.
32. His, pp. 131–44 and 145–55.
33. His, p. 147, 148.
34. His, p. 152.
35. His, Das Princip der organbildenden Keimbezirke und die Verwandschaften der Gewebe, *Archiv für Anatomie und Physiologie. Anatomische Abtheilung* (1901); 307–37.
36. Frequent references to His occur in the American work, mostly to the principle and to *Unsere Körperform*.
37. On M.B.L. history see Jane Maienschein, 'A Marine Laboratory for America:

Early History of the M.B.L.', paper delivered at the M.B.L., 1984, and on deposit in the archives there.
For more of the flavour of popular debates at the time see the Marine Biological Laboratory's *Biological Lectures*.
For examples of the different emphasis in England, see G. C. Bourne, Epigenesis or Evolution, *Science Progress* (1894) **1**, 105–26;
St George Mivart, Critical Remarks on the Theories of Epigenesis and Evolution, *Science Progress* (1894) **1**, 501–8.

38. Whitman, The Embryology of *Clepsine*, *Quarterly Journal of Microscopical Science* (1878) **18**: 215–315; citation p. 263.
39. On Whitman and his concerns, see the useful study by Jeffrey Werdinger, *Embryology at Woods Hole: The Emergence of a New American Biology*, doctoral dissertation, Indiana University, 1980.
40. Whitman, Changes Preliminary to Cleavage in the Egg of Clepsine, *Proceedings of the American Association for the Advancement of Science* (1878) **27**, 263–70; citation pp. 263–6.
41. Whitman, A Contribution to the History of the Germ-layers in *Clepsine*, *Journal of Morphology* (1887) **1**, 105–82; p. 107; E. B. Wilson, The Germ Bands of *Lumbricus*, *Journal of Morphology* (1887) **1**, 183–97.
42. Whitman, 'A Contribution,' p. 111.
43. Whitman, 'A Contribution,' pp. 138–40.
44. Whitman, 'A Contribution,' p. 169.
45. Whitman, The Kinetic Phenomena of the Egg during Maturation and Fecundation (Oökinesis), *Journal of Morphology* (1898) **1**, 227–52; citation, p. 227.
46. Whitman, The Seat of Formative and Regenerative Energy, *Journal of Morphology* (1888) **2**, 27–49; pp. 30, 38.
47. Whitman, Oökinesis.
48. Whitman, Evolution and Epigenesis, *Biological Lectures* (1895) 1894: 205–24; p. 209.
49. Whitman, Evolution, pp. 221–4.
50. Charles Otis Whitman, Evolution and Epigenesis, p. 211.
51. Whitman, p. 221.
52. Whitman, p. 224.
53. Whitman's contributions to the Marine Biological Laboratory's *Annual Reports* and his letters in the M.B.L. archives reflect this attitude, for example.
54. For more on Whitman and influences on him, see Jeffrey Werdinger, *Embryology at Woods Hole: The Emergence of a New American Biology*, especially Chapters 1 and 6.
55. Edmund Beecher Wilson, The Cell-Lineage of *Nereis*: A Contribution to the Cytogeny of the Annelid Body, *Journal of Morphology* (1892) **6**, 361–480.
56. Wilson, *The Cell in Development and Inheritance* (New York: Johnson Reprint Corporation, 1966; original 1896), pp. 328–9.
57. Wilson, 1896, p. 330.
58. For discussion of Wilson, see Alice Levine Baxter, *Edmund Beecher Wilson and the Problem of Development: From the Germ Layer Theory to the Chromosome Theory of Inheritance*, Ph.D. dissertation, Yale University, 1974;

Jane Maienschein, Shifting Assumptions in American Biology: Embryology, 1890–1910, *Journal of the History of Biology* (1981) **14**, 89–113;
Maienschein, What Determines Sex? A Study of Converging Research Approaches, *Isis* (1984) 75: 457–80; Werdinger, Chapters 2 and 7.
59. Baxter, Edmund B. Wilson as a Preformationist, p. 30.
60. Wilson, The Problem of Development, *Science* (1905) **21**, 281–94; citation p. 282.
61. Wilson, 1905, p. 288.
62. Wilson, 1905, p. 288.
63. Wilson, 1905, pp. 290, 292. See Baxter for further interpretation of Wilson's views.
64. See Frederick Churchill and Garland Allen, this volume, for discussion of the separation of heredity and development. Also, Churchill, William Johannsen and the genotype concept, *Journal of the History of Biology* (1974) **7**, 5–30.
65. Conklin, Cleavage and Differentiation, p. 30.
66. Conklin, Mosaic *vs.* Equipotential Development, *American Naturalist* (1933) **67**, 289–97; citation pp. 295–6.
67. Conklin, Cleavage and Differentiation, p. 19.
68. Conklin, pp. 28–9.
69. Conklin, *Heredity and Environment* (Princeton: Princeton University Press, 1915), pp. 83, 84–5; (Princeton, 1930), pp. 57–60.
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