

have been explored without an understanding of molecular problems that were not even broached until the 1950's. Although the data of geneticists ultimately forced embryologists from the Weismannian view of inheritance, this difficulty separated embryologists from geneticists during the period in which both matured as experimental sciences.<sup>16</sup>

The reluctance of embryologists to embrace Mendelian genetics had a profound effect on the development of evolutionary theory. The celebrated Modern Synthesis, through which Mendelian genetics was wedded to systematics, was an event in which embryologists played virtually no role. The difficulties which originally separated embryologists and geneticists were issues left unaddressed. The Modern Synthesis codified Mendelian genetics in terms of populations of individuals. Explicit in these formulations was the assumption that individuals could be treated as genetically homogeneous units. John Maynard Smith clearly articulates the assumption and its source in Weismannian thought, noting that:

After the publication of Darwin's *Origin of Species*, but before the general acceptance of Weismann's views, problems of evolution and development were inextricably bound up with one another. One consequence of Weismann's concept of the separation of the germ line and soma was to make it possible to understand genetics, and hence evolution, without understanding development. In the short run this was an immensely valuable contribution, because the problems of heredity proved to be soluble, whereas those of development

16. The extent to which the field of genetics was at odds with embryology is reflected in an anecdote recounted by Viktor Hamburger in his commentary on the minimal impact of embryological thought in the framing of the Modern Synthesis (in E. Mayr and W. B. Provine, eds. *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Cambridge, Mass.: Harvard University Press, 1980:97-112). Hamburger notes that: "Morgan's book *Embryology and Genetics* illustrates the ambiguity of this situation. In its preface, Morgan wrote: 'The story of genetics has been so interwoven with that of experimental embryology that the two can now, to some extent, be told as a single story. . . . It is possible to attempt to weave them together in a single narrative.' The story goes that after the publication of the book, Morgan asked a prominent visitor what he thought of it. The visitor frankly responded that he could not find a synthesis of the two fields; whereupon Morgan, tongue in cheek, asked 'What does the title say?' " (pp. 100-101).

apparently were not. . . . My own view is that development remains one of the most important problems of biology, and that we shall need new concepts before we can understand it. It is comforting, meanwhile, that Weismann was right."<sup>17</sup>

Weismann, however, was right for the wrong reasons. Yet his doctrine became a tacit assumption of the Modern Synthesis. The view of the individual adopted by the synthetic theory is that of Weismann. The individual is held to be a discrete unit, with heritability limited to a very small subset of genetically homogeneous cells. This view is not only derived from an erroneous theory—a theory implying that only some cells contain DNA—but it is also a view which is at considerable variance with the established facts of development.

### III

George Gaylord Simpson, one of the principal authors of the Modern Synthesis, schematized the assumption of genetic individuality in an explicit form, labeling it as Weismann's doctrine.<sup>18</sup> Many of us first encountered a version of Simpson's figure in secondary school (Figure 1.1). This now-classic view has the zygote producing somatic cells via mitosis and germ cells via meiosis. Genetic variation arising during the course of ontogeny cannot be inherited. Heritable variation only occurs in the zygote or during the reduction divisions of gametogenesis. This is an appealing diagram. It represents the ideal of the individual as a unique, genetically homogeneous, entity. It is an ideal, however, that is only approximated in real organisms.

Multicellular organisms are composites. Individuals are composed of cells capable of division and of variation. Within eukaryotic cells are organelles, also capable of reproduction and variation, and within organelles and nuclei are gene sequences which may also have these capabilities. As Weismann recognized, *heritability is controlled by development*. A unicellular alga dividing by mitosis to produce a clone of

17. Maynard Smith, J. *Evolution and the Theory of Games*. Cambridge University Press, 1982:6.

18. Simpson, G. G., C. S. Pittendrigh, and L. H. Tiffany. *Life: An Introduction to Biology*. New York: Harcourt, Brace, and Co., 1957:281.

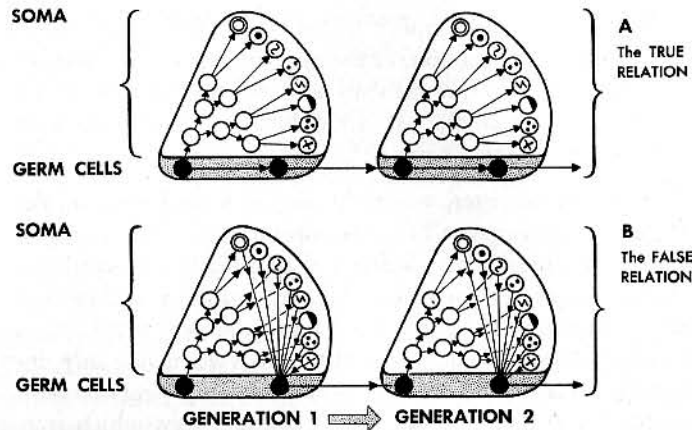


FIGURE 1.1 Schematic diagram of Weismann's doctrine from George Gaylord Simpson's influential textbook *Life: An Introduction to Biology*. Here somatic cells (variously filled circles) arise by mitosis and germ cells (closed circles in shaded region) by meiosis. This view excludes heritability of variants which arise in stem cells (open circles). (From Simpson, Pittendrigh, and Tiffany, 1957.)

daughter cells differs from a metazoan zygote dividing by mitosis likewise to produce a clone of cells in that all descendants of the former are capable of giving rise to a new multicellular individual, whereas only a fraction of the clonemates of the latter retain this ability. Irreversible differentiation of cells to purely somatic function denies a lineage the capacity to generate a new organism. Unless a cell lineage produces a gamete or retains totipotency and succeeds in asexually producing a new organism capable of further propagation, genetic variation within that cell lineage will not be heritable.

Heredity as studied today is a matter of macromolecules, information, and code. However intriguing the newly discovered fluidity of the genome, knowledge of the molecular mechanics of heredity is *not* equivalent to knowledge of the units which prove heritable. Recognition that the processes of development control heritability focuses the issue of inheritance from questions directed purely at the molecular mechanisms of transmission to questions of patterns in developmental determinism. If modes of development are such that only a few cell divisions are intercalated between fertil-

ization and the terminal determination of the germ line each generation, then the opportunity for heritable variation to arise in the course of ontogeny is small and the view of the individual as a genetically homogeneous unit is largely vindicated. If, however, patterns in development allow substantive opportunities for embryonic cells to vary and yet still gain access to the gametes, then genetic variation arising during the ontogeny of an individual must be acknowledged as a potentially important source of transmissible variation.

The fact that development controls heritability may be illustrated by comparing the development of two common laboratory animals. Consider first the development of the dipteran *Drosophila melanogaster* (Figure 1.2). Following fertilization and syngamy, the egg nucleus undergoes thirteen cleavage divisions in rapid sequence. The *Drosophila* egg, like any egg, has two sources of mRNA to draw upon; that drawn from the cytoplasm and provided by the mother, and that synthesized by the embryo itself. In *Drosophila*, the first appreciable mRNA synthesis by the embryo is found only after the thirteenth cleavage division. Development prior to this point is entirely directed by instructions left by the parent.<sup>19</sup> These first thirteen cleavage divisions are not accompanied by cell division; the embryo at this stage is a coenocytic mass. Following the thirteenth nuclear division, however, cell division takes place and the resulting embryo is composed of two distinct regions: the pole cells and the cellular blastoderm. The pole cells are the primordial germ cells and the roughly 6,000 cells comprising the cellular blastoderm are the somatic cells. It is at this point in devel-

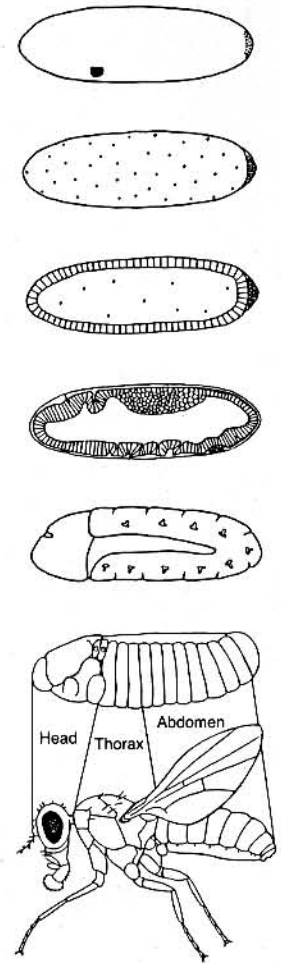


FIGURE 1.2 Stages in the development of *Drosophila melanogaster*. (After Slack, 1983 and Raff and Kaufman, 1983.)

19. Using a wide variety of techniques, several investigators have confirmed that the *Drosophila* embryo displays an exceedingly low rate of RNA synthesis prior to blastoderm formation (e.g., Fausto-Sterling, A., L. M. Zheutlin, and P. R. Brown. 1974. *Dev. Biol.* 40:78-83). That this small, but detectable, RNA synthesis is not fully responsible for germ cell determination is demonstrated by the occurrence of maternal effect mutants acting during early determination (Rice, T. B. and A. Garen. 1975. *Dev. Biol.* 43:277-286). Eggs, for example, bearing one of these, *mat(3)1*, form no somatic blastoderm, but normal pole cells. The extent of maternal control is confirmed by nuclear transplantation experiments which demonstrate that nuclei are totipotent prior to blastoderm cellularization (Illmensee, K. 1972. *Wilhelm Roux' Arch. Entwicklungsmech.* 170:267-298; Okada, M., I. A. Kleinman, and H. A. Schneiderman. 1974. *Dev. Biol.* 39:286-294).

opment that determination of cell fate takes place for larval, as well as adult, structure.

Only thirteen nuclear divisions are intercalated between the zygote and the terminal determination of those cells destined to become the zygotes of the next generation. A variant would have to arise within this brief interval in order to be heritable. But since development up to this point is directed solely by maternal instructions, there is no opportunity during the entire life cycle of *Drosophila* for any cell to influence its own fate by products of its own making. Simpson's scheme is vindicated, as the germ is derived directly from the zygote under maternal instructions, generation after generation.

Contrast *Drosophila* development with that of the simple freshwater hydroid *Hydra* (Figure 1.3). The zygote gives rise to an embryo composed of two distinct populations of cells: the interstitial (or I-cells) and somatic cells. The I-cells are a multipotent cell lineage which may, under the proper stimulus, give rise to any of the various somatic cell types.<sup>20</sup> Some somatic cell types are capable of further cell division and growth, some are not. The latter category of somatic cells must be continuously replenished by differentiation of I-cells. Both classes of somatic cells, however, share an inability to either differentiate into different somatic cell types or to return to the multipotent status of I-cells.

The zygote of a *Hydra* gives rise to a polyp which, under favorable conditions, will reproduce asexually. Asexual reproduction involves the movement of multipotent I-cells and various somatic tissues into a bud off the parent polyp. This bud soon detaches and assumes an independent existence. The asexual reproductive phase may be of indeterminate length; investigators maintain stock asexually for decades. When local conditions deteriorate, *Hydra* may be induced to cease reproduction by asexual iteration, and instead I-cells differentiate into gametes. However, between

20. Interstitial cells, recognized by their distinctive amoeboid morphology, have been observed to give rise to various somatic lineages in several hydroids. Gross morphological identity has traditionally formed the basis for the assumption that these cells represent a single multipotent lineage. Hans Bode and others are actively testing the possibility that the morphological identity of interstitial cells may mask an underlying complex of partially differentiated stem cells (as, for example, is the case in lymphocytes).

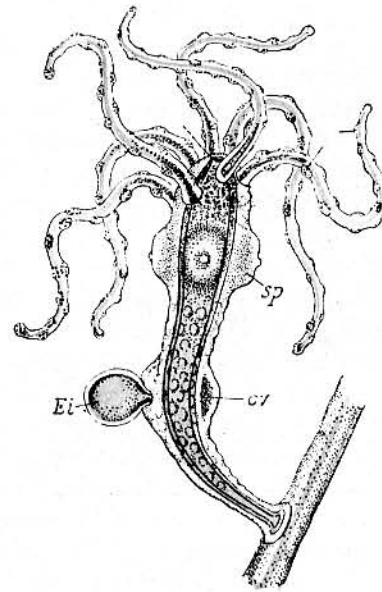


FIGURE 1.3 Polyp of *Hydra viridis*, showing testis (sp), ovary (ov), and developing embryo (Ei). (From Weismann, 1904.)

each sexual generation an indeterminate number of asexual iterations may occur. In contrast to *Drosophila*, where totipotency is limited after thirteen nuclear divisions, the I-cells of *Hydra* remain multipotent and mitotically active throughout the potentially great life span of the animal.

The *Drosophila* example fits Simpson's figure well, the *Hydra* hardly at all. Simpson's figure may be modified, as in Figure 1.4, to accommodate hydroids. The modified view holds that the zygote gives rise, by mitosis, to a totipotent cell lineage which may have one of three fates: (1) it may give rise to somatic cells, (2) it may undergo reduction divisions and give rise to gametes, or (3) it may retain totipotency and undergo continuing episodes of differentiation into somatic cells or gametes.

Now let us consider the potential for heritability of sub-organismal variation in these two developmental modes. Any variant arising in the totipotent lineage is in the pool from which the gametes are drawn. The likelihood that a genetic variant will occur in this pool of cells is a function of the basal rate at which variation arises per division and the

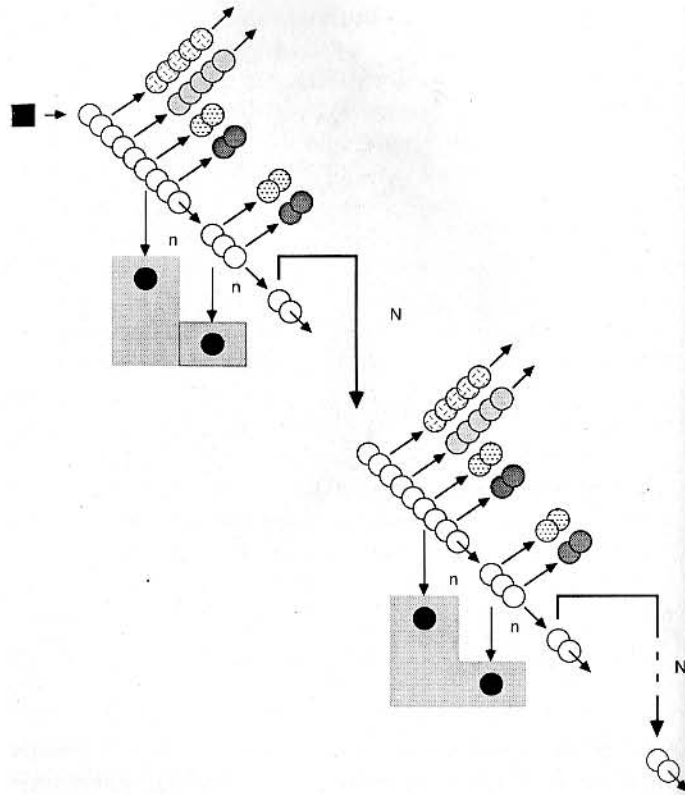


FIGURE 1.4 Modification of Simpson's schematic diagram (Figure 1.1) which recognizes the ability of totipotent stem cells (open circles) to give rise to gametes (closed circles) and recognizes the potential for repeated asexual iteration of new physiologically discrete individuals from a single zygote (closed box). The number of totipotent divisions per sexual generation ( $n$ ) and the number of asexual generations per sexual generation ( $N$ ) varies in a taxon-specific fashion and may be very large. This figure represents a conservative modification of Simpson's diagram as it does not permit functional somatic cells (variously filled circles) to contribute to the gametes, a process known to occur in some metazoans (see Figure 3.4).

number of divisions made by the totipotent lineage.<sup>21</sup> In *Drosophila melanogaster*, for example, the totipotent lineage undergoes thirteen nuclear divisions per sexual generation. The potential that a variant will arise is very low indeed. In *Hydra*, the totipotent lineage may undergo an astronomical number of divisions before sexuality occurs. In dipterans such as *Drosophila*, it is appropriate to view the individual as a unique, genetically homogeneous, unit. It is highly unlikely that genetic variation will arise and gain access to the gametes within a single generation. In the hydroids, however, the number of divisions of the totipotent cell line intercalated between each sexual generation is so high that it is very likely that genetic variation will both arise and be inherited. In one case it is appropriate to view the individual as a genetically homogeneous unit and treat variation within a population without considering variation within individuals. In the other, it is not.

The individual as a genetically homogeneous unit is an ideal which is approximated to varying degrees in different taxa as a function of the mode of development of the particular taxa in question. It is of some importance, then, to identify phyletic patterns in developmental mode. This information is available. Embryologists of the late nineteenth century and, to a lesser extent, the twentieth century described patterns in development in great detail. Likewise, the embryologists of the twentieth century, with an experimental approach to development, have clearly pinpointed the timing and extent of multipotency in various lineages. This information is precisely that which the Modern Synthesis failed to accommodate.

21. The basal rate of change in base-pair sequence per cell is certainly not a constant, but likely varies as a complex taxon-specific function of the state of differentiation of the cell in question (e.g., B-lymphocytes in the mouse thymus have greatly accelerated mutation rates). Therefore, it is dangerous to presume that an estimate of genetic variation can be made solely on the basis of differences in the number of cell divisions, unless—as in this example—the differences are of astronomical proportions.

Taxon-specific differences in error rate may reflect the maintenance of traits which act either to generate or to minimize variation within the context of a particular developmental mode. In this regard, it is particularly intriguing that transposable elements (whose transposition generates considerable variation) are active only in the germ line of *Drosophila*, which makes few heritable divisions per generation, whereas transposable elements are active only in somatic cells of maize, which makes large numbers of heritable divisions per generation.

It is convenient to recognize three modes of development: somatic embryogenesis, epigenesis, and preformation.<sup>22</sup> In somatic embryogenesis, a distinct germ line is lacking. Rather, one cell lineage is capable of both participation in somatic function as a stem cell lineage and is also competent to give rise to gametes throughout ontogeny (e.g., plants). In contrast, organisms with epigenetic development possess a clearly differentiated germ line, but the germ line only appears after the primordia of major organ systems of the adult have become established (e.g., annelids). At the extreme end of this spectrum in the ontogenetic timing of the terminal determination of the germ line are organisms with preformistic development. Here the germ line is terminally differentiated in earliest ontogeny, often under direction of maternal-derived determinants deposited in the egg (e.g., nematodes).

The phyletic distribution of these modes of development is presented in Table 1.1 for all multicellular, cellular-differentiating taxa. The phyletic pattern is intriguing. Somatic embryogenesis is by far the most common mode of development. With the exception of the Volvaceles, all multicellular representatives of the Kingdom Protista possess somatic embryogenic development. All members of the Kingdom Fungi and the Kingdom Plantae do as well. Only representatives of the Kingdom Animalia possess epigenetic and preformistic development, and these two modes of development are by no means ubiquitous. No fewer than nine animal phyla display somatic embryogenesis.

The ideal of the individual as an entity that may be treated as genetically uniform is at best an approximation. It is apparent that individuality is a derived character, approximated closely only in certain taxa. This fact is of substantial interest, for it means that not only is it inaccurate to consider the individual as the sole unit of inheritance in most taxa, but also that we have little assurance that it is appropriate to assume this to have been the case throughout geological time, even in those taxa in which individuality is now closely approximated.

22. The term "totipotent" is used here to refer to any cell which retains the capacity to produce both gametes and somatic cells.

TABLE 1.1 Phyletic Distribution of Developmental Mode<sup>1</sup>

Taxon <sup>2</sup>	Cellular Differentiation <sup>3</sup>	Developmental Mode <sup>4</sup>
PROTOCTISTA		
Phaeophyta	+/-	s
Rhodophyta	+/-	s
Chlorophyta	+/-	p
Ciliophora	+/-	s
Labyrinthulamycota	+/-	s
Acrasiumycota	+/-	s
Myxomycota	+/-	s
Oomycota	+	s
FUNGI		
Zygomycota	+	s
Ascomycota	+	s
Basidiomycota	+	s
Deuteromycota	+	s
PLANTAE		
Bryophyta	+	s
Lycopodophyta	+	s
Sphenophyta	+	s
Pteridophyta	+	s
Cycadophyta	+	s
Coniferophyta	+	s
Angiospermophyta	+	s
ANIMALIA		
Placozoa	+	s
Porifera	+	s
Cnidaria	+	s
Ctenophora	+	p
Mesozoa	+	p
Platyhelminthes	+	s, e, p
Nemertina	+	e
Gnathostomulida	+	u
Gastrotricha	+	p
Rotifera	+	p
Kinorhyncha	+	u
Acanthocephala	+	p
Entoprocta	+	s
Nematoda	+	p
Nematomorpha	+	u
Bryozoa	+	s
Phoronida	+	s
Brachiopoda	+	u

TABLE 1.1 (cont.)

Taxon <sup>2</sup>	Cellular Differentiation <sup>3</sup>	Developmental Mode <sup>4</sup>
ANIMALIA		
Mollusca	+	e, p
Priapulida	+	u
Sipuncula	+	u
Echiura	+	u
Annelida	+	s, e, p
Tardigrada	+	p
Onychophora	+	p
Arthropoda	+	e, p
Pogonophora	+	u
Echinodermata	+	e
Chaetognatha	+	p
Hemichordata	+	s, e
Chordata	+	e, p

1. After Buss (1983, *Proc. Nat. Acad. Sci. USA* 80:1387-1391).

2. Taxonomic divisions after L. Margulis and K. V. Schwartz (*Five Kingdoms*, San Francisco: Freeman, 1982). Although several of the phyletic distinctions advocated in this book are not traditional, this work has the merit of allowing the reader to consult a single text for an introduction to each group.

3. + = present in all known cases; +/- = presence in some cases and absence in others.

4. s = somatic embryogenesis; e = epigenetic; p = preformistic; u = unknown. The use of the terms epigenetic and preformistic refer only to the determination of the germ line and are not meant to recall the divisive debate on preformation of a century ago.

#### IV

It is one of the more remarkable oversights in biology that the patterns in developmental determinism just outlined failed to become incorporated into the Modern Synthesis. The lack of communication between geneticists, whose concern throughout this century has been with the mechanics of inheritance, and embryologists, whose concern has been with patterns in cellular differentiation, was clearly central. It is nevertheless astounding that the geneticists and natural historians forging the synthesis brought none of these developmental concerns to the fore.

At least two factors are of significance here. The first is largely a function of the organisms with which the framers of the Modern Synthesis worked. Virtually all of the early

genetic discoveries were the work of botanists: the concept of mutation from deVries, the distinction between phenotype and genotype from Johannsen, linkage from Bateson's work on peas, multifactor inheritance from Nilsson-Ehle on wheat, and, of course, Mendel's peas. Later genetic work has also been profoundly influenced by botanists: for example, inversions and translocations from McClintock, genetic systems from Darlington, and polyploidy from Stebbins. However, sandwiched between these two periods of botanical pre-eminence was the central problem of the development and testing of the chromosome theory. This was the activity that dominated genetic work in the period just before the beginning of the Modern Synthesis (1910-1925). The central discoveries—that genes lie on chromosomes and that mutations occur in genes—were made using *Drosophila*. Accomplishments during this critical pre-synthesis period occurred in zoology. Similarly, the natural historians central in the development of the Modern Synthesis were largely zoologists. Dobzhansky worked on *Drosophila*; Mayr, Simpson, and Rensch on birds and mammals. Dipterans and vertebrates were the areas of expertise of the individuals who framed the synthesis. This zoological bias is particularly revealing. The geneticists who made the discoveries precipitating the synthesis, the mathematicians trained by these geneticists, and the natural historians recognizing their relevance to systematics and evolution, *all worked on organisms with preformistic development*. Fruit flies, mice, and humans are all organisms with early embryonic determination of the germ line—all are organisms in which the notion of the individual as a genetically homogeneous unit of selection is closely approximated. Thus neither geneticists nor evolutionists had reason to bring developmental concerns to the problems broached by the Modern Synthesis.

Just as the Modern Synthesis was unattended by embryologists, so did it pass untouched by botanists, mycologists, and zoologists of colonial invertebrates. The first botanical work applying the synthetic approach, G. Ledyard Stebbins's *Variation and Evolution in Plants*, did not appear until 1950.<sup>23</sup> Why did botanists, mycologists, and zoologists of

23. The expansion of the Modern Synthesis to clonal invertebrates is an even more recent development. That individual zooids or polyps within a colony are not equivalent to individuals in a genetic sense was only widely discussed following the publication in 1973 of *Animal Colonies* (Board-