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Generic physical mechanisms of morphogenesis and pattern formation as determinants in the evolution of multicellular organization

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Abstract. Early embryos of metazoan species are subject to the same set of physical forces and interactions as any small parcels of semi-solid material, living or nonliving. It is proposed that such "generic" properties of embryonic tissues have played a major role in the evolution of biological form and pattern by providing an array of morphological templates, during the early stages of metazoan phylogeny, upon which natural selection could act. The generic physical mechanisms considered include sedimentation, diffusion, and reaction–diffusion coupling, all of which can give rise to chemical nonuniformities (including periodic patterns) in eggs and small multicellular aggregates, and differential adhesion, which can lead to the formation of boundaries of non-mixing between adjacent cell populations. Generic mechanisms that produce chemical patterns, acting in concern with the capacity of cells to modulate their adhesivity (presumed to be a primitive, defining property of metazoa), could lead to multilayered gastrulae of various types, segmental organization, and many of the other distinguishing characteristics of extant and extinct metazoan body plans. Similar generic mechanisms, acting on small tissue primordia during and subsequent to the establishment of the major body plans, could have given rise to the forms of organs, such as the vertebrate limbs. Generic physical processes acting on a single system of cells and cell products can often produce a widely divergent set of morphological phenotypes, and these are proposed to be the raw material of the evolution of form. The establishment of any ecologically successful form by these mechanisms will be followed, under this hypothesis, by a period of genetic evolution, in which the recruitment of gene products to produce the "generically templated" morphologies by redundant pathways would be favoured by intense selection, leading to extensive genetic change with little impact on the fossil record. In this view, the stabilizing and reinforcing functions of natural selection are more important than its ability to effect incremental change in morphology. Aspects of evolution which are problematic from the standard neo-Darwinian viewpoint, or not considered within that framework, but which follow in a straightforward fashion from the view presented here, include the beginnings of an understanding of why organisms have the structure and appearance they' do, why homoplasy (the recurrent evolution of certain forms) is so prevalent, why evolution has the tempo and mode it does ("punctuated equilibrium"), and why a "rapid" burst of morphological evolution occurred so soon after the origin of the metazoa.

Keywords. Metazoa; origin of form; developmental templates.

> *Development starts from a more or less spherical egg, and from this there develops an animal which is anything but spherical .... One cannot account for this by any theory which confines itself to chemical statements, such as that genes control the synthesis of particular proteins. Somehow or other we must find how to bring into the story the physical forces which are necessary to push the material about into the appropriate places and mould it into the correct shapes.*
>
> C H Waddington
> *The Nature of Life* (1961)

1. Introduction

Discussions of biological development and evolution often assume that the genome of each multicellular organism contains a set of instructions for the generation of the organisms overall form and the pattern of arrangement of its tissues. The origin of novel, heritable morphological phenotypes is, in this view, considered to be due to alterations in the hypothesized 'genetic program' brought about by random mutations in the germ-line DNA. Morphological evolution, *i.e*. the establishment of new morphological phenotypes at the population level, is attributed solely to differential reproductive success of the randomly produced variants, with the implication that the mechanisms of selection are entirely disconnected from those that generate variation. Thus, extant morphological phenotypes, while acknowledged to be subject to the laws of physics and chemistry, are held to owe their structural organization to the immediate physical environment to no greater degree than do machines, such as clocks or automobiles.

There are few *a priori* constraints on the kinds of morphological phenotypes that are possible when development is considered to be dictated by a genetic program. Much as a sophisticated computer graphics program can represent any conceivable structure on a video screen, a genetic program would seem to be capable of generating any arbitrary arrangement of proteins, polysaccharides, nucleic acids, lipids, minerals, and even metals, all of which may participate in biochemical pathways. Given enough time, anything is possible. If there are any reasons, apart from time limitations, for the absence of reproducing chain saws or compact disc players among the Earth's organisms, they are not contained in the genetic program concept.

More recently this extreme viewpoint has been tempered by the recognition that random genetic changes do not lead to equally random phenotypic changes. Because the array of viable forms that can be generated by embryological mechanisms is limited, phenotypic variation is said to be subject to 'developmental constraints' (Gould and Lewontin 1979). But developmental mechanisms themselves must have come into existence sometime after the evolution of cellular life. Did they arise purely by chance, or was their emergence in some sense 'inevitable'? One possible answer to this question is the suggestion that basic mechanisms of morphogenesis and pattern formation inescapably arise from properties of cell aggregates considered as physical matter. The implication is that biological forms and patterns, particularly in the early embryo, are to an important extent predictable from the interactions of such matter with the immediate physical environment. This is a concept that has some precedents in the scientific literature, in the work of D'A rcy W Thompson (1942) for example. But because of the non-obvious connection of this idea to genetic analyses of both development and evolution, it has been relegated to the margins of biology during most of this century. This is unfortunate, because, as will be discussed below, the recognition that certain morphogenetic and pattern forming mechanisms are physically inevitable is entirely consistent with our understanding of gene-dependent biological processes. Moreover, unlike the standard notion of a randomly arrived at genetic program for the construction of organisms, this idea can provide insight into the question of why organisms are organized in the fashion they are.

2. Deficiencies of the 'genetic program' metaphor

The genetic program concept of development is widely held and taught [*e.g*. 'We know that the instructions for how the egg develops are written in the linear sequence of bases along the DNA of the germ cells' (Watson et al 1987)], although it has also been criticized (Wright and Davison 1980; Hubbard 1982; Webster and Goodwin 1982; Oyama 1985; Stent 1985; Newman 1988; Nijhout 1990), and it is doubtful whether it has ever played a significant role in elucidating any developmental mechanism. Each embryonic cell that will participate in forming the *somatic* or bodily structures of an organism contains a virtually identical set of DNA sequences. Some of these sequences correspond to, and provide templates for, the sequences of RNA molecules that perform various structural and catalytic functions in the cell, and help specify the primary structure of all of the organism's proteins. Since DNA segments are selectively expressed in each cell type, the differential regulation of gene activity through time and space is a central problem of developmental biology, and the one the genetic program metaphor was invented to explain.

It is clear that during development the set of biochemical and physical conditions that prevails in the embryo at any moment can lead to changes in composition and distribution of cellular components. These, in turn, bring about a new set of biochemical and physical conditions, leading to further changes. Genes, as the embryo's record of the primary sequences of the RNAs and proteins it can produce, are essential participants in this cascade of reactions, but they in no way embody a program for them. The deficiency of this metaphor extends well beyond the inability of DNA *per se* to act as the program's storage medium. The concept of a program, understood as an intricately organized set of instructions acting on a collection of variables to bring about a well-defined outcome, would not be particularly helpful in characterizing development even if the 'software' were considered to include cellular components such as ions, vitamins and water, and not only the genes and what they specify. Just because a process (such as embryogenesis) has a reliably repeated outcome does not require that its behaviour be specified by a set of instructions. The return of Halley's comet to our solar system every 76 years depends on precise physical interactions, but on no instructions or program.

In addition to being a misleading post-hoc description of the results of developmental investigations, the genetic program idea may encourage misconceived research strategies. For example, the notion that form and pattern are coherently represented like a map in each of the embryo's cells, and biologically realized as a point-to-point 'interpretation' by the genome of a simple, chemically defined coordinate system (Wolpert 1969), raises the hope that a small set of genes, such as those that specify proteins containing the `homeobox' DNA binding motif, might provide a 'Rosetta Stone' for pattern formation (Slack 1984). Indeed, one frequently expressed rationale for the Human Genome Initiative is the expectation that a comprehensive knowledge of the relative locations of DNA sequences will reveal the instructions for embryonic development (DeLisi 1988).

3. Generic physical processes as organizing principles of biological form and pattern

In his book *On growth and form*, D'Arcy Thompson (1942) considered the role of

physical forces in the generation of biological patterns and structures: Cell and tissue, shell and bone, leaf and flower, are so many portions of matter, and it is in obedience to the laws of physics that their particles have been moved, moulded and conformed' His attempts to explain structure–function relationships and evolutionary modification of biological form in terms of physical and mathematical laws led to a number of striking insights. For example, features of the vertebrate skeletal system, ranging in scale from the gross anatomy of the spinal column to the microscopic configuration of trabeculae in spongy bone, were seen to resemble the arrangement of load-bearing elements in a cantilever bridge. In addition, differences in body shapes of related fish could be derived from one another by simple coordinate transformations that were plausibly tied to different strategies of accommodation to external forces, such as friction.

Unfortunately, D'Arcy Thompson largely neglected mechanisms of development and inheritance, both of which were subjects of vigorous research during the period of his work. This certainly contributed to the failure of his important ideas to enter the mainstream of biology. Even if a structure can be rationalized on the basis of forces acting on adult forms, this provides little insight into the generation of such a structure. Why, for example, should skeletal elements become arranged during development in utero in a manner appropriate to bearing weight, when the fluid environment ensures that the developing bones are rarely exposed to such stresses? Baldwin (1902) proposed a process of 'organic selection' by virtue of which fortuitously appearing gene combinations which produced a structure identical to one that would be produced by mechanical factors would be advantageous, and spread through the population. In a similar fashion Waddington (1957) demonstrated how a purely 'physiological' response to environmental stimuli might be incorporated into an organism's developmental repertoire under certain circumstances, a mechanism he referred to as 'genetic assimilation'. Simpson (1953) considered this class of phenomena (which he referred to as the 'Baldwin effect') to be a 'relatively minor outcome of the theory [of evolution by natural selection]'. In contrast, I will suggest that a generalization of this effect, and the recognition that its influence on organisms differed at different stages of their evolutionary history, necessitate a thoroughgoing revision of the neo-Darwinian paradigm.

Leaving aside, for the moment, the puzzle of the initial evolution of embryonic development of traits whose only rationale is in the biology of the adult form, we can consider correspondences in the embryo itself between organismal structure and 'external' influences. Unlike adult organisms, the forms and functions of which are of a scale, composition, and level of integration that make them resistant to gross transformation by simple physical effects, embryos are at least potentially subject to such forces. This was recognized by Balfour (1885) as early as 1875, when he observed that `... there is no question that during their embryonic existence animals are more susceptible to external forces than after they have become fully grown', and, following the first edition of *On growth and form* in 1917, Needham (1936) called for an extension of D'Arcy Thompson's analysis to the realm of embryology.

Studies using this approach have subsequently appeared sporadically in the scientific literature. Steinberg and his coworkers have shown, for example, that isolated embryonic tissue fragments round up, take on 'equilibrium' shapes, and spread upon and engulf one another, as if they were immiscible elasticoviscous

liquid droplets with characteristic surface tensions (Steinberg 1978; Steinberg and Poole 1982). Morphogenetic phenomena such as *gastrulation,* the formation of a new layer of embryonic tissue by the intrusion of the edge of a cell sheet between two pre-existing layers, can thus be viewed as occurring for reasons similar to the `wetting' (De Gennes 1985; Forgacs *et al* 1989) by one fluid of the interface between a second fluid and its substratum (figure 1, see also Phillips and Davis 1978).

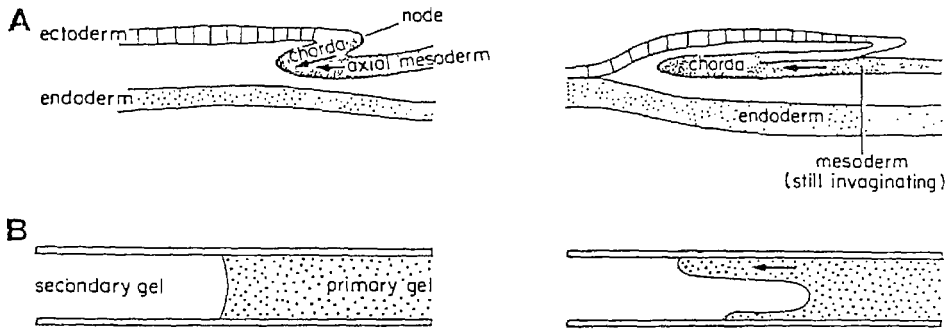

Figure 1. (A) Stages in mammalian gastrulation viewed in median section. *Left*: Axial mesoderm has begun to enter the primitive pit, farming. the notochordal process, or chorda. *Right*: Chorda advances beneath the ectoderm followed by additional mesoderm, which then spreads laterally (out of the plane of section). Redrawn from Deuchar (1975). (B) Spreading and rearrangement by `matrix-driven translocation' of two partially assembled type I collagen gels between two parallel polystyrene plates (Newman *et al* 1985; Forgacs *et al* 1989). Primary gel contains heparin-coated cell-sized polystyrene latex beads. Secondary gel contains the heparin-binding adhesive glycoprotein fibronectin. Relative movement of the two matrix regions is dependent on `phase separation' of the two gels and differential adhesion.

Gravity is another physical force that has been proposed to play a role in early development. For example, Ancel and Vintemberger (1948) suggested that the ooplasmic rearrangement that occurs following fertilization in the eggs of anuran amphibians might be caused by density differences (figure 2). *Diffusion* is usually thought of as a process by which uniform distributions of chemical substances are brought about, but . Turing (1952) demonstrated that the kinetic coupling of diffusion with chemical reaction or biosynthesis can lead to nonuniform concentration distributions of reactants. One possible outcome is *striping,* the establishment of parallel bands of a chemical substance separated by bands lacking that substance (figure 3). A demonstration of the Turing phenomenon in nonliving polymer gels has recently been described (Castets et al 1990), and this pattern forming mechanism has been shown to be biochemically plausible in several animal and plant systems (Gierer and Meinhardt 1972; Kauffman *et al* 1978; Lacalli and Harrison 1978; Newman and Frisch 1979; Harrison and Hillier 1985; Meinhardt 1988; Newman *et al* 1988).

We have called phenomena such as surface tension, phase separation, gravity, and reaction–diffusion coupling 'generics' physical mechanisms of morphogenesis and pattern formation, to emphasize their broad applicability to living and nonliving systems (Newman and Comper 1990). Generic mechanisms are contrasted

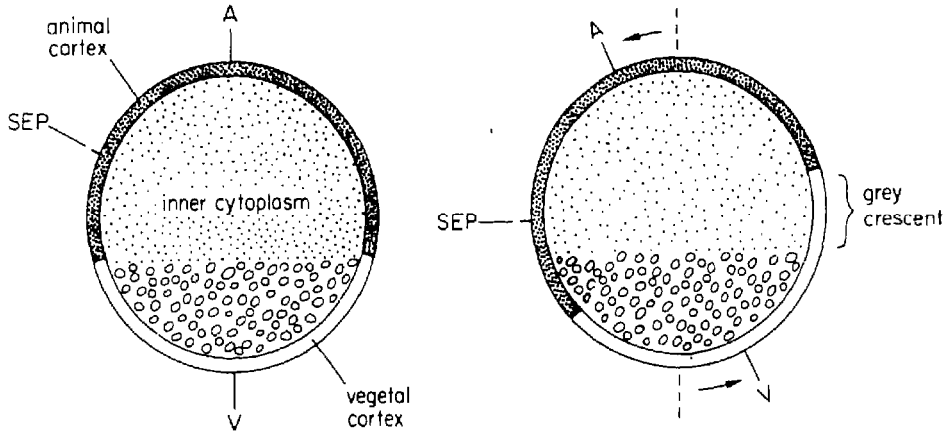

Figure 2. The cortical/cytoplasmic rotation in anuran amphibian embryos. A 30° rotation of the cortex relative to the inner cytoplasm is required for normal dorsoventral polarity to be established. Diagrammatic sections are shown before (*left*) and after (*right*) rotation. The cortex rotates so that the sperm entry point (SEP) moves vegetally. The grey crescent visible in *Rana pipiens* embryos is formed by the overlapping of pigmented animal hemisphere cytoplasm by nonpigmented vegetal hemisphere cytoplasm. Redrawn from Elinson and Rowning (1988).

to 'genetic' processes, a term we have reserved for a distinct phenomenon in biological systems: assemblies of intricately organized macromolecules that have coevolved to carry out highly specific functions, *e.g*. cytoplasmic 'motors' (Vale 1987), regulated membrane channels (Hille 1984), or gene promoter elements and

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Figure 3. Chemical wave generation by a reaction--diffusion mechanism, and examples of stripe patterns during development. (**A**–**E**) Graphical representation of chemical wave formation, based on Maynard Smith (1968). It is assumed that two substances, **A** and **B**, which influence one another's synthesis, are produced throughout a row of cells, and that there is a balance in the rates of synthesis and utilization of **A** and **B** (*i.e*. they are at a *steady state*). The steady state shown in panel A is *spatially uniform*: the concentrations of both **A** and **B** are unvarying along the row of cells. Under certain conditions a *spatially nonuniform* stationary state (panel **E**) can be achieved by the growth and stabilization of a fluctuation (panels **B**–**D**) (Turing 1952). The following conditions are sufficient to bring about this phenomenon: substance **A** has a positive effect on the synthesis of both itself and substance **B**; substance **B** has an inhibitory effect on the synthesis of **A**; the diffusion rate of **B** is greater than that of **A**. Arrow in panel **C** indicates the point at which a reduction of the concentration of **A** to below its uniform steady state level will be initiated on the basis of the assumptions above. The number of peaks and valleys of **A** and **B** that will be in place when the system finally reaches the new steady state will depend on reaction and diffusion rates, the size and shape of the spatial domain in which these events are occurring, and the modes of utilization of **A** and **B** at the boundaries of the domain. See Turing (1952), Maynard Smith (1968) and Newman and Comper (1990) for further details. (**F**) *Drosophila* blastoderm stage embryo showing early *even-skipped* protein pattern (stippled stripes). Based on Frasch *et al* (1987). (**G**) Progress of chondrogenesis in the chick wing bud between days 4 and 7 of development. Solid black regions represent definitive cartilage; stippled areas represent early cartilage. Stages arc those of Hamburger and Hamilton (1951). Pane] **G** from Newman and Frisch (1979), copyright 1979 by the **AAAS**.

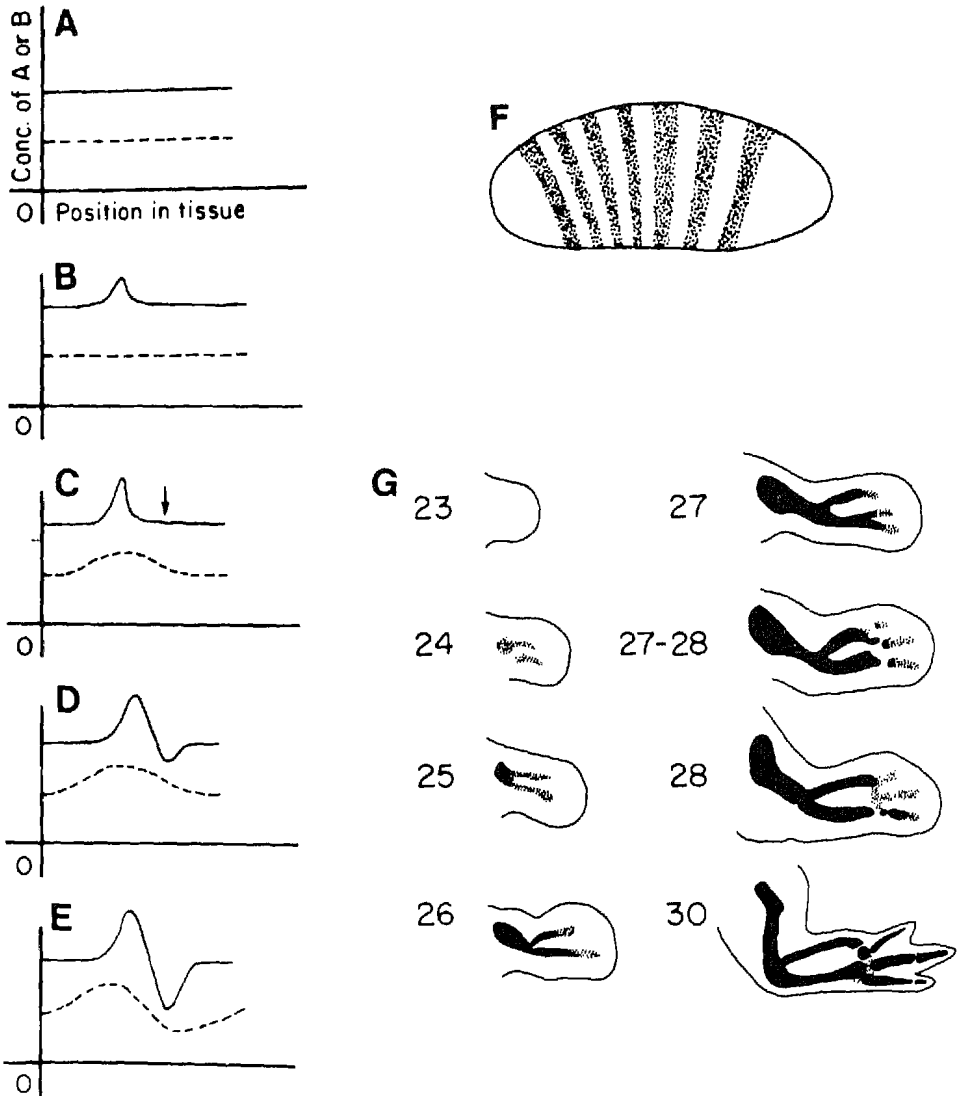

Figure 3.

their associated *trans*-acting regulatory factors (Goto et al 1989; Stanojevic *et al* 1989). Because generic physical mechanisms are plausible determinants of many morphological features of early embryos, it is reasonable to hypothesize that they play important developmental roles. But when this notion has been put to the experimental test the story turns out to be less straightforward.

4. Morphogenesis and pattern formation are not simply generic

In several cases that have been studied in detail, it has been found that patterns and forms that could potentially be determined by generic physical effects are driven (in

addition? exclusively?) by intricate, highly evolved molecular machinery. After fertilization in the amphibian egg, for example, there is a 30° rotation of the dense cortical cytoplasm relative to the less dense deeper cytoplasm. In some species this rotation has the effect of revealing a lightly pigmented region of deep cytoplasm on one side of the egg, the 'grey crescent'. This region, or its equivalent, marks the future dorsal area of the embryo (figure 2). As noted above, Ancel and Vintemberger (1948) suggested that the relatively rigid egg cortex, upon mechanical release from the underlying cytoplasmic core midway during the first cell cycle, slips to one side under the influence of gravity in normally oriented eggs. The ability of unit gravity to effect a proper overlap between cortical and deep cytoplasm in eggs whose normal rotation is inhibited by UV light (Neff et al 1984) is consistent with a role for gravity in normal axis specification. However, a mechanism of axis specification driven exclusively by gravity is contradicted by results of Vincent *et al* (1986), who embedded *Xenopus* eggs in gelatin so that the cortex could not move, and found that the cytoplasmic core, including the denser vegetal regions, rotated up one side of the cortex by 30°, working against gravity. Clearly the egg must also have a means other than gravity to drive the rotation. The presence of an oriented array of microtubules in the shear plane between the cortex and subcortical cytoplasm (Elinson and Rowning 1988) suggests that the force-generating mechanism might be similar to the energy-consuming microtubule-dependent organelle transport systems found in other cell types (Vale 1987).

Another phenomenon that has been hypothesized to be due, at least in part, to a generic physical mechanism is the formation of striped patterns of expression of the primary 'pair-rule' genes in *Drosophila* embryos. The pattern of expression depicted for the even-skipped product shown in figure 3b would seem to be a likely candidate for explanation by a Turing-type mechanism, and indeed it has been the subject of several such models (Lacalli et al 1988; Meinhardt 1988). Nonetheless, experiments in which pair-rule genes with mutated promoter sequences were introduced as 'P-elements' into *Drosophila* embryos and subsequently expressed have demonstrated convincingly that individual stripes, rather than arising collectively from a generic dynamical process, are each specified by a unique complex of DNA binding proteins acting in *trans* to activate stripe-specific promoters (Goto et al 1989; Stanojevic et al 1989). These regulatory proteins, which include the 'gap' gene products, are not themselves distributed in a striped pattern, but as simpler gradients. In contrast to the self-organizing stripe-forming processes represented by Turing-type mechanisms, the recent genetic results point to the embryo's use of Rube Goldbergian molecular machinery for 'making stripes inelegantly' (Akam 1989).

What are the implications of the recognition that whereas organisms *could* produce their major morphological and patterning features by generic mechanisms, contemporary organisms rarely exhibit such simple developmental processes? It is likely that the complexity of modern ontogeny is centrally tied to the fact that organisms are the results of evolutionary processes (Bonner 1988). Indeed the evolution of organisms virtually assures that their structural and functional organization will often be `overdetermined', the outcome of several relatively independent mechanisms. This 'suspenders and belt' phenomenon is familiar to all students of experimental embryology, and is highly relevant to the question of whether generic physical mechanisms contribute importantly to determining why organisms are organized in characteristic ways.

5. Why do organisms look the way they do?

The evolution of a novel form or pattern must occur in the context of all previously existing properties of an organism. That the eggs of most marine organisms are spherical, for example, must originally have had something to do with the fact that the equilibrium configuration of a droplet of cytoplasm surrounded by a lipid membrane, immersed in an aqueous medium, is a sphere. The evolution of cytoskeletal proteins and the elaboration of cytoarchitecture resistant to mechanical deformation would certainly be of selective advantage to phylogenetic lineages in which they occurred. It makes sense to think of this evolution of genes and the associated genetically based structures as having been guided by generic forces: eggs that were both generically *and* genetically determined to take on a spherical shape would be much more likely to maintain this shape in the face of environmental change than those formed *only* by generic forces. Lineages represented by such organisms may indeed evolve to a point where the cytoarchitecture becomes more important *functionally* in determining the egg's shape than do the egg's equilibrium properties as a droplet of fluid. However, if we want to understand why the egg looks like it does, we must understand the origin of the shape, and the nature of the generic 'template' that presumably guided the evolution of the cytoarchitectural support system.

Conservation and reinforcement of 'successful' forms by gene evolution would contribute to morphological stasis in phylogenetic lineages, but radical changes in body plan could also be precipitated by small genetic changes that happened to bring new external forces into play. During early evolution of multicellular forms these external forces would often be generic physical processes. It is plausible, for example, that the biochemical evolution of yolk phosphoproteins was driven mainly by selection for efficiency of nutrient storage. However, the resulting yolk platelets would sediment within the egg by virtue of their incidental property of having greater density than other cytoplasmic components, and, for the phylogenetic lineages that evolved them, serve as a basis for spatial differentiation within the oocyte and any multicellular form to which it gave rise.

In larger tissue masses an analogous harnessing of generic physical effects could also have taken place. For instance, Holtfreter (1943a) demonstrated that amphibian endodermal cells containing an endogenous surface coat will spread over uncoated endoderm, and conversely, an aggregate of uncoated endoderm will sink into a layer of coated endoderm. Such effects may serve to initiate gastrulation in the hollow sphere that constitutes the early amphibian embryo (Holtfreter 1943b, 1944). Steinberg (1978) and Steinberg and Poole (1982) interpreted such engulfment phenomena as arising from adhesivity–cohesivity differentials, and suggested that even *quantitative* differences in intercellular adhesive strengths are enough to bring these effects into play. Recent experiments have verified this conclusion (Friedlander *et al* 1 989).Whatever stabilizing machinery may have subsequently evolved to ensure the reliability of gastrulation under a wide variety of environmental conditions, it is plausible that the generic mechanism of differential adhesion was the origin of cellular ingress and tissue invagination in multicellular aggregates.

Another illuminating example involves the recognition that, whereas the products of as many as 25 different genes appear to be involved in the segmentation of the *Drosophila* body plan (Ingham 1988), it is inconceivable that this network could have arisen *de novo* during evolution. In fact, this system is redundant and overdetermined. This

can be seen, for instance, in the interaction of *nanos* and *hunchback*, two of the genes in the segmentation regulatory network. The gene product of *nanos* apparently serves only to repress the translation of mRNA specified by the maternal *hunchback* gene (Irish *et al* 1989). Embryos that lack both maternal *hunchback* gene product and a functional *nanos* gene develop in an apparently normal fashion, although the loss of *nanos* alone is lethal (Hulskamp *et al* 1989).

The formation of chemical stripes in the early embryos of ancestors of *Drosophila* could have been due originally to a Turing-type reaction–diffusion mechanism if (i) there were an appropriate ratio between the spatial scale of the tissue domain to be so organized and the diffusivities of candidate morphogens, and (ii) at least some of the putative morphogens positively enhanced their own synthesis. Each of these conditions apparently holds for some systems in contemporary *Drosophila* embryos (Frasch and Levine 1987; Hiromi and Gehring 1987). Cellular release (and thus the potential for diffusion) of growth and differentiation factors, and autostimulation of the production of such factors, may have evolved separately as means for large-scale coordination of tissue function and for amplification of signals. When appropriately tuned, biochemical circuits with *both* these features can spontaneously form stripes. Such stripes may have been fortuitously advantageous in promoting, say redundancy of structure in the insect's wormlike ancestor. The problem with reaction–diffusion coupling as a mechanism for such patterning is that it is temperature-dependent (as are all diffusion-based processes), often sensitive to domain size and shape, and thus generally unreliable. The superimposition by genetic evolution of reinforcing circuitry for the generically produced pattern would undoubtedly have favoured certain phylogenetic sublineages, although such evolution would not, in general, be reflected in the morphological fossil record.

The central hypothesis proposed here is that virtually all morphogenetic and patterning effects seen during early development (see Gilbert 1991 for a review) can, *in principle*, result from the action of generic processes on embryonic cells or tissues. *Ooplasmic rearrangement* could have its origin in density differences of physically distinct intracellular determinants. Tissue immiscibility and the engulfment and spreading effects resulting from differential adhesion could have been the origin of a variety of morphogenetic movements, including *epiboly*, the concerted movement of epithelial sheets to enclose deeper layers of the embryo; *invagination*, the infolding of a region of tissue, like the indenting of a rubber ball; *involution*, the inturning of an expanding outer layer so that it spreads over the internal surface of the remaining external cells; ingression, the migration of individual cells from the surface layers into the interior of the embryo; and *delamination*, the splitting of one cellular sheet into two or more parallel sheets. Convective effects, particularly in conjunction with gravity or surface tension, can give rise to *microfingering*, the interpenetration of parallel protrusions of distinct cytoplasmic materials or tissues (Newman and Comper 1990). And reaction–diffusion mechanisms could have provided the original basis for the *striping* that underlies certain segmental patterns, as described above.

The implication of all of this is that organismal morphology is not arbitrary–simply the result of undirected molecular tinkering. Organisms look the way they do, *i.e*. are recognizable as organisms, because the generic processes that templated their morphologies early during their evolution are only capable of giving rise to a limited array of forms and patterns. These, in turn, are embodied in a certain type of object, an organism.

While it is all but impossible to reconstruct the phylogeny of present-day developmental mechanisms, it may be feasible to experimentally 'deconstruct' modern organisms to determine the minimal requirements for generating specific forms or patterns. Putative secondarily acquired or coopted genetic reinforcements for morphogenetic processes could be removed by mutation (as in the studies of the *nanos*/*hunchback* system) (Hülskamp *et al* 1989; Irish *et al* 1989), or by specific drugs directed, for example, against cytoplasmic motors (Vale 1987). In many cases the organism may have evolved to a point at which its early embryo is no longer susceptible to the forces that originally engendered a given pattern or form. But in other cases the relevant morphogenetic effect might still occur, albeit roughly or unreliably.

6. Implications of generic–genetic coupling for the evolution of early development

The previous discussion suggests that at some fundamental level the embryonic organization of organisms is an almost predictable function of the physical world of which they are a part. Morphological evolution, at least during the early radiation of multicellular forms, can be viewed in terms of the reiterative application of a small set of generic physical processes. Prior to the evolution of a high degree of genetic reinforcement of a particular subset of forms, a vast array of morphologies must have been possible. But all such forms would have had the stamp of the generic processes and forces to which semisolid, chemically reactive matter is subject: gravity, adhesion, surface tension, convection, and the interaction between reaction and diffusion.

The view outlined here has a number of implications, both specific and general:

(1) *Some form of gastrulation will be among the earliest evolutionary manifestations of metazoan development*. Multicellularity presupposes that a cell-surface system mediating intercellular adhesion already exists. Indeed, such a system must be the defining characteristic of the original metazoa (Bonner 1988). To ensure that a cell cluster forms an undistorted sphere, strict regullation of the quantittive strength of this adhesion would be required. But in the absence of such tight controls, random attenuation of adhesive strength would cause individual cells to slough off, or alternatively, burrow within the aggregate, as in *multipolar ingression*. If a *patch* of cells in the aggregate were all to exhibit reduced adhesive strength (perhaps by virtue of having incorporated some inhibitory substance that was nonuniformly distributed in the cytoplasm of the aggregate's founder cell), *unipolar ingression* of individual cells would be likely. If the cells of the patch were more strongly adhesive to each other than were the surrounding cells, *emboly*, or inpocketing, would occur (figure 4). It should be noted that the capacity to undergo one or another of these types of gastrulation would be *inherited* not as a genetic program, but rather as the outcome of generic physicochemical effects acting on multicellular aggregates.

In his discussion of the possible origin of gastrulation, Buss (1987) proposes that the protistan world was the arena of a conflict between cell lineages 'in their quest for increased replication' in the face of a constraint against simultaneous ciliation and cell division. Gastrulae, or multilayered organisms, are held to be the solution to this `problems'. In contrast to this notion, I suggest that gastrulation is the inevitable consequence of nonuniform adhesive interactions in solid or hollow cell aggregates.

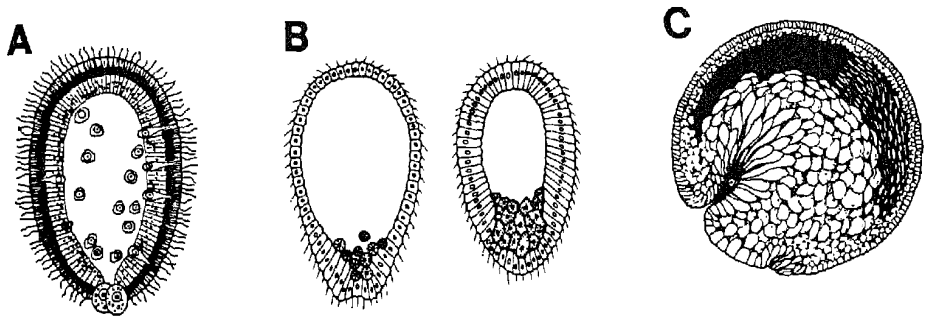

Figure 4. Different modes of gastrulation: (**A**) multipolar introgression, in the sponge *Leucosolenia blanca* (from Minchin 1900); (**B**) two stages of unipolar introgression, in the hydroid *Aqueorea forskalea* (from Bergner 1971); (**C**) emboly, in the amphibian *Amblystoma punctatum* (from Holtfreter 19436).

The significance of the resulting forms for the origin of biological individuality, as persuasively laid out by Buss, would certainly pertain. Gastrulae would arise, however, not as the solution to a preexisting problem, but inescapably, as loci of new biological possibilities.

(ii) *Once organisms with a multiple germ layer organization had evolved, a wide spectrunt of body types would have become possible*. Molecular mechanisms for the establishment of tissue segregation or immiscibility by differential adhesion, a generic requirement for gastrulation according to the hypothesis above, could be used reiteratively to create additional tissue boundaries and independent cell lineages. For this to occur in a reproducible fashion, factors that influenced the quantitative expression of cellular adhesion molecules would need to become nonuniformly distributed. This might happen as the result of sedimentation of cytoplasmic determinants in the colony's founder cell, for example, or by appropriately tuned reaction—diffusion coupling between cell products that are positively autoregulating and ones that are secreted and diffusible. The profusion of metazoan body forms found in the Precambrian Ediacara formation (Glaessner 1984; Fedonkin 1985) and in the Burgess Shale formation from the Middle Cambrian period (Whittington 1985; Gould 1989) can plausibly be seen as manifestations of an exploration of the particular universe of morphological phenotypes generated in primitive embryos by the iteration and permutation of a small number of generic physical processes.

(iii) *The evolutionary persistence of a subset of morphological phenotypes will depend not only on the relative adaptation of body forms to ecological conditions, but also on the facility with which genetic mechanisms can be recruited to stabilize and reinforce such forms.* It is expected that morphogenetic mechanisms based on generic forces such as gravity, surface tension and reaction—diffusion effects would produce outcomes relatively sensitive to externalities like orientation and temperature. We can postulate a kind of 'covert evolution' by which molecular processes of the organism that predated the origin of a generically conditioned morphology might become linked to the production of that same morphology by random mutation of DNA and protein structure. This could lead to integration of various subsystems

with little morphological consequence. In this model, random genetic change does not produce a biological form by increment. The form, presumed to have been brought about by generic forces, and to have established itself in the ecosystem, already exists. Natural selection in this covertly evolving population would not be based on ecological discrimination among minor morphological differences, but on the ability to maintain successful morphological phenotypes in changing environments (*i.e*., Schmalhausen's 1949 'stabilizing selection'). But the more genetic mechanisms are mobilized for the preservation of a particular morphology, the less the developmental pathway in question will be divertible by environmental perturbation. This phenomenon has been termed 'canalization' by Waddington (1957), and 'autoregulation' by Schmalhausen (1949). Put another way, after the initial profusion of body forms morphological innovation will be more and more the exception; *selection will typically he for morphological stasis*.

The palaeontological data on the profusion of body forms during early metazoan evolution are consistent with this view. The amount of time separating the earliest known unicellular eukaryotes (approximately 1.4 billion years ago) from the earliest recognizable members of extant metazoan phyla (from the Precambrian Ediacara formation) is about 700 million years. By 100 million years later, all extant phyla were apparently established. Yet in the 600 million years that separated the Cambrian from the Recent, no new body plans arose (Glaessner 1984; Fedonkin 1985; Whittington 1985; Gould 1989).

(iv) *Certain body plans arising during the original phase of 'morphological profusion' would be intrinsically more susceptible to reinforcement and stabilization by genetic mechanisms than others, leading to a culling of the original array of morphologies in changing environments.* Although this is a speculation that needs to be tested by appropriate modelling, the following example can serve to illustrate what is meant. Reaction–diffusion processes can readily give rise to stripes, spots or spirals (Harrison and Hillier 1985; Gould 1989) of a diffusible molecule. Were such a molecule to induce the enhanced expression of a cell adhesion molecule, a patterned set of 'compartments', with no cell mixing across boundaries, would form. Thus any of these pattern types could define an embryonic *bauplan*. Let us assume that some of these *bauplans* suited organisms for reproductive success, or for the occupation of a particular ecological niche. A body plan based on a striping mechanism could be readily reinforced and stabilized by multiple promoter elements in *cis* to the gene specifying the protein in question (Goto *et al* 1989; Stanojevic et al 1989), which could readily arise by random mutational events. For instance, if other factors were present that were, for incidental reasons (gravity, diffusion), distributed in simple gradients in the direction orthogonal to the stripes, promoters that were activated by a combination of such factors so as to reinforce a given stripe would be retained by stabilizing selection, whereas promoters that disrupted the generically templated striping pattern would be selected against. The evolution of analogous molecular mechanisms to reinforce and stabilize a particular set of spots or spirals would be much more formidable. A segmental body plan, which could originally have been set on its evolutionary path by a stripe-forming process, might thus be more susceptible to genetic stabilization, and thus evolutionarily more persistent, than a `checkerboard' or a 'pinwheel' plan, which may originally have been established by spot-forming or spiral-forming processes.

It is significant that many of the metazoan body plans of the Ediacaran fauna

(some indeed reminiscent of checkerboards and pinwheels) (Glaessner 1984; Fedonkin 1985) and a large proportion of those from the later Burgess Shale fossil bed (Whittington 1985; Gould 1989) defy placement into any of the thirty or so currently extant phyla. Taken together with the failure of new *bauplans* to emerge since that period, it appears that a large proportion of viable body plans fell by the wayside after their emergence during the 'Cambrian explosion'. This culling may have been purely serendipitous, as has been suggested (Gould 1989). Alternatively, it could have resulted from an intrinsic bias in the capacity of random gene mutation to evolve stabilizing mechanisms for certain generically produced morphologies.

(v) *Phylogenetic lineages unable to make use of a particular generic mechanism of development would have a profoundly different evolutionary history front lineages for which all such mechanisms were available.* The acquisition of rigid cell walls by some taxa would make the generic processes based on tissue fluidity and differential adhesion less important in setting trends for morphogenetic change. The early separation of plant and animal kingdoms once multicellular forms became established may reflect a division based primarily on the foreclosure of this important generic mechanism of development in the plant lineages.

(vi) *At any particular stage of generic/genetic coevolution, more than one developmental pathway, leading to quite distinct body types, may be available to the developing organism.* This is exemplified by the phenomenon of the *phenocopy* in Drosophila, in which a wild-type fly that experiences a temperature or chemical perturbation as an embryo, without undergoing genetic alteration develops to resemble a mutant fly (Goldschmidt 1938). An even more striking set of examples is provided by organisms, ranging from insects, to tunicates, to amphibians, that undergo metamorphosis. This phenomenon demonstrates that different body forms are compatible with a single genotype (Matsuda 1987). (These can be radically different, as seen in tunicate metamorphosis, where a chordate-like larva is transformed into a sessile adult with no obvious axial organization.) Moreover, as the phenomenon of 'direct development' in sea urchins (Raff 1987) or frogs (Elinson 1987) demonstrates, the larval forms are not obligatory precursors to the adult forms, as would be suggested on the view that development occurs according to a ’genetic program'. With the concept of generic/genetic coupling, the existence of divergent pathways of morphogenesis and pattern formation in genetically identical individuals is to be expected, as is the possibility of changes in the order of expression of such pathways (`heterochrony') (Gould 1977). Direct development, instead of being considered the result of the evolutionary 'loss' of the set of steps that leads to the larval stages (Raff 1987), might be more productively analysed in terms of the action of generically based processes of early development in a different physical context [*e.g*. a much larger egg (Raff 1987; Elinson 1987)]. Of course, at present this viewpoint represents indications for further study rather than a set of conclusions.

7. Generic physical effects in later ontogeny and phylogeny

Once the major features of metazoan body organization became established and genetically reinforced, the locus of further morphological evolution would, if the

view described above is correct, shift to small tissue primordia which were physically susceptible to generic physical effects similar to those that previously guided the development of the embryo as a whole. This corresponds to the phase of *organogenesis* that follows the establishment of the body plan in the more elaborate phyla. If we are concerned merely with form and pattern, the generic mechanisms may indeed be identical to some of those seen to be virtually inevitable in the developing egg: differential adhesion and reaction–diffusion coupling. (Gravity would probably have a negligible role at these later stages.)

To take one example of organ formation, the developing vertebrate limb, the acquisition of differential adhesivity by subpopulations of cells along the body wall has plausibly been proposed as the mechanism by which the limb buds individuate as blobs of tissue immiscible with the surrounding flank (Heintzelman *et al* 1978). Moreover, a reaction–diffusion mechanism, based on the autostimulatory activity of a TGF-*ß*-like morphogen, coupled with the ability of this factor to stimulate production of the adhesion protein fibronectin, has been proposed to account for the pattern of skeletal elements (Newman and Frisch 1979; Newman *et al* 1988; Leonard *et al* 1991) (figure 5). It is significant that this mechanism of limb skeletal pattern formation implies that the number of parallel elements that develop at any proximodistal level in the limb can vary by the simple agency of increase or decrease in the anteroposterior dimension of the limb bud (Newman and Frisch 1979). If this is true, then abrupt changes in limb morphology during evolution need not be the result of gradual, incremental change. 'Jumps' between varieties with different digit numbers, for example, can occur in a single step, by virtue of tiny changes in the growth control of the limb buds (Newman 1984).

Like the inheritance of the body plan as a whole, the inheritance of the capacity to reproducibly form organs such as the limbs, heart, or kidneys, requires not a genomic representation of these structures, but rather the production of an appropriate set of components (tissue masses, for example) subject to relevant generic effects.

A feature which evidently took on increasing importance as organs became ever more elaborate is the process of *differentiation*. This was encountered earlier in this discussion as a matter of quantitative gene regulation by nonuniformly distributed factors, by which intercellular adhesion, for example, was modulated in strength. With the occasional duplication and random drift of the 'structural' or protein-specifying portion of a regulated gene, qualitative regulation of gene products specific to particular pattern elements (`segment identity' proteins in *Drosophila*, cartilage-type collagen, cardiac myosin) could be brought into play in a modular fashion (Mittenthal 1989), without disrupting the regulation of the ancestral gene.

The hypothesis that gene duplication was important in the evolution of differentiation is, of course, not new (Ohno 1970). In relation to the general framework presented here, however, some new implications emerge. The regulation of differentiation involves the *conditional* expression of genes. In the scenario described above for the evolution of gastrulation, intercellular adhesivity was modulated by spatially nonuniform intraembryonic factors that were put in place originally by generic effects such as sedimentation or reaction–diffusion coupling. The basic body plans and organ patterns would thus bear the stamp of generic processes pertaining to the small elasticoviscous fluid droplets that eggs and organ primordia are. This would remain so even if reinforcing and stabilizing genetic processes were eventually to 'take over', and by the processes of *heterostasy* (action

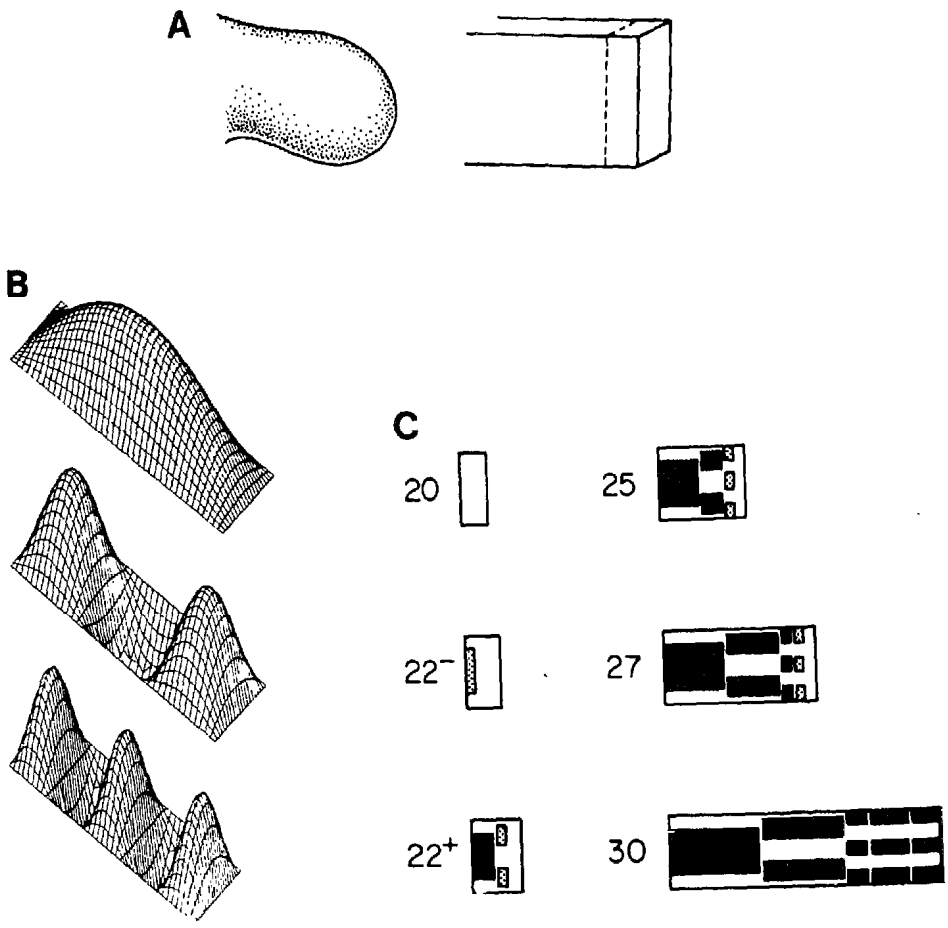

Figure 5. Interpretation of chick limb development based on reaction-diffusion mechanism. (**A**) *Left*: Drawing of a 5-day wing bud. Right: Schematic representation of 5-day wing bud with as yet unpatterned distal mesenchyme demarcated by dashed line. (**B**) *Top to bottom*: Graphs representing predicted distribution of TGF-ß and fibronectin in the prechondrogenic distal mesenchyme at three successive stages of development. (**C**) Predicted cartilage pattern based on schematic model. Figure from Newman and Comper (1990), based on Newman and Frisch (1979).

under changed conditions) and heterochrony, induce the generically templated pattern in the absence of the original determinant. In large adult animals, cell responses such as differentiation can also occur in response to 'generic' external effects appropriate to the scale of these larger objects. Thus, *weight-bearing*, by means of physiological adaptation mechanisms, induces reorganization of long-bone trabeculae, and *friction* induces thickening of the soles of the feet. Since these conditional responses to new generic effects may be reinforced by covert 'stabilizing' or 'canalizing' evolution, they can come to depend as much on reinforcing genetic mechanisms as on the original generic ones. As a result of heterostasy and heterochrony, features like bone trabeculae suitable for weight bearing (Thompson

1942) or thickened soles (Mittenthal 1989) can be induced in *utero*, in the absence of the generic processes that originally caused them. This process, termed 'genetic assimilation' by Waddington (1957), is thus a special case of generic/genetic coupling, applicable to later stages of evolution.

8. Homoplasy and the genetics of morphological change

The viewpoint discussed above suggests strongly that the initiation of major morphological change during evolution depends upon the early embryo, or upon organ primordia of comparable size and composition to the early embryo, becoming susceptible to fresh generic effects. This could be due either to genetic modification of an organism, or to an alteration in its environment. Morphological changes brought about by environmental effects would become heritable only if the new environment were relatively permanent (and therefore itself inherited) Oyama 1985; Johnston and Gottlieb 1990). Morphological changes brought about by genetic mutation in an unchanged environment would, of course, also be inherited. But, if the ideas presented here are valid, such changes can only be of a relatively limited variety. Indeed, if the generic mechanisms that may be brought into play during early development include only gravity, surface tension and related phase separation phenomena, reaction–diffusion coupling, and convection, we might expect to see additional manifestations in the new body plans of gradients and stripes, of 'compartments' defined by adhesive differentials conforming to such chemical prepatterns, and perhaps of microfingers, brought about by interfacial tension or density differentials. Beyond this, it is difficult to imagine what else might arise. After the capacity for cells to specialize with regard to functions other than adhesion had evolved, we would expect to see organs in which differentiated tissues (*e.g.* muscle, cartilage) were arranged according to patterns originally templated by gradients or stripes of chemical concentration, or by the spreading and engulfment effects of differential adhesion. In essence, the vast majority of random genetic changes with overt effects on form or pattern would have consequences that, regardless of how profound they were, would also be stereotypical.

Taken together with the proposal, discussed in an earlier section, that genetic changes of a canalizing or stabilizing nature would be the ones most readily retained by natural selection, the stereotypical nature of morphological alterations that may indeed arise by mutation implies that there will be only a loose connection between gene evolution and morphological evolution. Although the presumed strength of such a connection has long been a tenet of neo-Darwinism, it continues to come up against incompatible findings. A recent study analysed inherited differences in the morphology of the mandible in inbred strains of mice in relation to the genetic divergence between the strains. It was concluded that there was little correspondence between morphological and genetic divergence (Atchley *et al* 1988). Another recent study demonstrated that extensive morphological evolution in fish had taken place in a period of about 200,000 years with only minor genetic change (Meyer *et al* 1990). Such findings are entirely consistent with, and indeed expected on the basis of, the concept of generic/genetic interaction presented here.

Homoplasy is morphological similarity of a feature in divergent lineages whose common ancestor was not similar to either lineage in this trait. For example, a

reduction in the number of hind-limb digits from five to four has occurred independently in three different lineages of plethodontid salamanders (Wake and Larson 1987). Such phenomena have traditionally (within the neo-Darwinian framework) been considered to result from convergent evolution based on functional adaptation to similar environments. If homoplasy is rare, the expectation is that morphological divergence will provide an accurate assessment of genealogical relationships. But, in fact, homoplasy is rampant in salamander taxa (Duellman and Trueb 1986; Wake 1991), and recent extensive revisions, based on nucleic acid data, of the phylogenetic trees for these amphibia embody hypotheses that require extensive convergence and supposed reversals in the evolution of morphological phenotypes (Duellman and Trueb 1986; Wake 1991). And there is no reason to chink, that these taxa are exceptional with regard to their degree of homoplasy (Sanderson and Donoghue 1989).

I want to propose here that homoplasy is as pervasive as it appears to be because morphological features are generically templated. Instead of being viewed as an exception to an expected concordance of 'morphological distance' with 'genetic distance', homoplasy should be seen rather as the exploration by various sublineages of a delimited universe of morphological phenotypes. Such exploration would account for the profusion of body forms at the Precambrian/Cambrian transition, but also encompass later phenomena like the explosive speciation of fish in Lake Victoria (Meyer *et al* 1990) and the genealogically uncorrelated morphological divergence of mandible form (Atchley *et al* 1988), of which homoplasy can be considered an extreme case. This interpretation generalizes the notion of `developmental constraint' in the determination of adaptively inexplicable structures (Gould and Lewontin 1979), by incorporating the hypothesized basis of the `developmental rules' themselves. Thus, while agreeing with the statement of Wake and Larson (1987) that convergent evolution may represent recurrent 'production of discrete alternative phenotypes that are intrinsic to the generative system', I would go further, and say that the generative systems themselves are, in an important sense, intrinsic to the material properties of early embryos and organ primordia. On this basis we might hope to explain not only why certain morphological variations show up recurrently in parallel lineages, but why body plans, and the various organs and appendages, took the forms they did in the first place.

9. Conclusions

I have presented a view of the relationship between development and evolution that entails significant departures from the standard neo-Darwinian model. The new view utilizes the distinction between 'generic' and 'genetic' mechanisms of development (Newman and Comper 1990) to synthesize the disparate insights of Baldwin (1902), Waddington (1957), Schmalhausen (1949) and D'Arcy Thompson (1942), among others, with recent findings on physical and molecular mechanisms of morphogenesis and pattern formation. If this view is correct, it provides the beginnings of an account of why biological organization has the particular character it does, and helps resolve certain difficulties with the neo-Darwinian view, such as the tempo and mode of evolutionary change (Gould and Eldredge 1977).

I will list the main elements of the framework outlined here, emphasizing, for clarity, the points of divergence from the standard neo-Darwinian picture. It should

be kept in mind, however, that nothing in the view presented here prohibits gradual morphological evolution by standard Darwinian mechanisms from taking place; such effects are just suggested to he of less importance than generally considered.

(i) Biological forms and patterns are 'generically templated' by physical processes acting on multicellular aggregates. These processes include rearrangement of ooplasmic determinants due to gravity, boundary formation, spreading and engulfment effects in tissues due to differential adhesion, and the formation of biochemical stripes due to reaction–diffusion coupling.

(ii) Numerous morphological phenotypes would be consistent with a given genotype, particularly during early stages of evolution. This is because the phenotype is not 'programmed' by the genotype, but arises from interactions between an organism containing a particular set of genes and a variable environment.

(iii) If some of the numerous possible phenotypes are well suited to survival and reproductive success, and are of a type to which genetic reinforcing mechanisms can be recruited by random mutation, relatively rapid, covert genetic evolution will take place, which will have the effect of making the expression of these phenotypes more reliable, and thus more *heritable*. Such evolution 'selects' preexisting, generically templated forms, rather than incrementally moving from one adaptive peak to another through nonadaptive intermediates.

(iv) Stabilizing evolution will make subsequent morphological evolution less likely. In addition, reinforcing genetic mechanisms can 'take over', by being triggered under different conditions (heterostasy), and at different times during development (heterochrony), thus bringing about an outcome that was originally generically templated in the absence of the original generic stimulus.

(v) Either minor genetic changes *or* environmental changes will bring about alterations in the spectrum of morphological phenotypes available to the organism. if they bring fresh generic processes into play. Like the alterations caused by genetic change, those induced by environmental change can become heritable if the new stimulus persists.

(vi) Initial speciation would take place with little or no genetic change. Subsequent genetic evolution would occur rapidly, but with little or no additional morphological diversification between the new taxa.

(vii) Minor morphological variations within modern species, such as those studied by Mendel, utilized by animal and plant breeders, and considered to be the raw material of macroevolution by Darwin, in actuality represent the limited scope of generic/genetic interactions in highly canalized taxa. Such variations would not be expected to lead to extensive morphological diversification.

A number of specific predictions, and explanations of well-accepted phenomena that are difficult to reconcile with the neo-Darwinian perspective, flow in a

straightforward fashion from the statements above:

(i) Gastrulation, of one form or another, is an inevitable consequence of multicellularity and differential adhesion, and should have arisen numerous times during early metazoan evolution.

(ii) Organisms with a wide spectrum of body plans (*e.g*. segmented, 'checkerboard', annular, and 'pinwheel') would all be expected to arise from the interaction of differential adhesion effects with gravity-driven and reaction–diffusion mechanisms, and to have proliferated during early metazoan evolution. But because only some of these *bauplans* would be susceptible to reinforcement by standard genetic mechanisms such as promoter selectivity, a culling from the original array would occur. Once significant stabilizing selection of the relevant body plans had taken place, no new ones would emerge.

(iii) Later structural specialization, including organogenesis in animals, would evolve by the action on small tissue primordia of some of the same generic mechanisms as those which originally acted on whole embryos. Generically templated organ forms and patterns (like generically templated *bauplans*) would initially be expressed in a highly diversified, but nonetheless stereotypical, fashion. Eventually, a subset of `reinforcement' morphologies will be stabilized by covert gene evolution and may come to be expressed during development in the absence of their original generic determinants.

(iv) *Homoplasy* and other discordances between genealogy and morphology would be the rule rather than the exception. Correspondingly, phylogenetic trees constructed on the basis of morphology alone would be inescapably flawed.

(v) The tempo of allelic change at the population level would vary as a function of the capacity of the external environment to elicit new morphological phenotypes. It would also be influenced by internally dictated possibilities for genetic reinforcement of some of these phenotypes. Because genetic variations would be retained or eliminated according to their ability to stabilize discrete morphological phenotypes, genetic evolution should tend to accelerate *after* major speciation events.

(vi) Evolution of basic body form, and of later structural specializations, would be characterized by rapid morphological diversification (in the absence of extensive genetic change) separated by long periods of morphological stasis (accompanied by a great deal of genetic change).

(vii) During early periods in the evolution of metazoa, before very extensive genetic stabilizing mechanisms for generic developmental processes had been acquired, development would have been more subject to environmental perturbation than is the case at present. Therefore global climate changes, which have occurred episodically during the history of life, would be expected to have led to mass extinctions of whole taxa, leaving others relatively untouched, by virtue of selective effects on early, vulnerable stages of development.

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