Genetics of Body Pattern Formation During Embryonic Development in *Drosophila melanogaster*

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1. Introduction

One of the major goals of modern biology is to understand how the complex body pattern of a plant or animal develops from a simple apparently undifferentiated egg. All multicellular organisms begin their life as a single cell which divides. These division products sooner or later acquire some special properties because of which different cells become differently specialized, both structurally and functionally. It is remarkable that the pattern of specialization that sets in at very specific time points in the history of development of an organism is also spatially specific, i.e., each cell in a developing embryo not only follows a time scale but also "knows" it location relative to specific reference points (like the posterior and anterior poles and dorsal or ventral sides). In a simple analogy, the process of development and differentiation can be compared to the construction of a building from simple-looking raw materials: the construction progresses in a very organized fashion according to the "blue-print" prepared by an architect. In the case of living organisms, this "blue-print" is expected to be inherited in every generation so that the species-specific form and functions are faithfully produced every time a zygote begins its life. Obviously, this "blue-print" is transmitted through generations in the form of biological information stored in genes.

Classical descriptive and experimental studies on embryonic development in a variety of higher organisms had laid down the foundations of our understanding of the process of development and differentiation but these studies in general failed to explain the underlying causes and mechanism of embryonic events. Since the process of development and differentiation had to have a genetic basis, it was the genetic approach which permitted unraveling of mystery of the remarkably orchestered, reproducible and species-specific pattern of development. It was because of genetic studies with *Drosophila* that a remarkably dramatic progress has been made in recent years in the field of developmental biology. Mutants affecting differentiation of specific structures of *Drosophila* were known for long. However, since these mutants in most cases affected adult structures, their study did not provide deeper insight into embryonic processes. Specific search for mutants that affect early embryonic development of *Drosophila* proved extremely rewarding (Nusslein-Volhard and Wieschaus, 1980; Nusslein-Volhard *et al*, 1984; Jurgens *et al*, 1984; Wieschaus *et al*, 1984; Schupbach and Wieschaus, 1986) since they allowed a direct approach to the genetic determinants of embryonic development. The genetic approach, combined with the power of molecular biological and recombinant DNA technique has made the subject of developmental biology all the more exciting. As a result of these studies, we now know a lot about the genetics of development, molecular nature of substances and the

mechanisms involved in determining body pattern. This article presents an overview of the genes and their functions that transform a fertilized egg of the fruit fly into an organised larva.

The body of an adult fly, (like most other insects) is metameric, meaning that it is made up of a linear array of serially repeated segments. A newly hatched larva hardly appears to have the same structure as an adult does. However, a closer look at its ventral cuticle reveals that it has the same number and linear arrangement of segments (Fig. 1). Each larval segment is easily distinguished (by its pattern of chitinous teeth) and differentiates into specific adult structures depending upon their position.

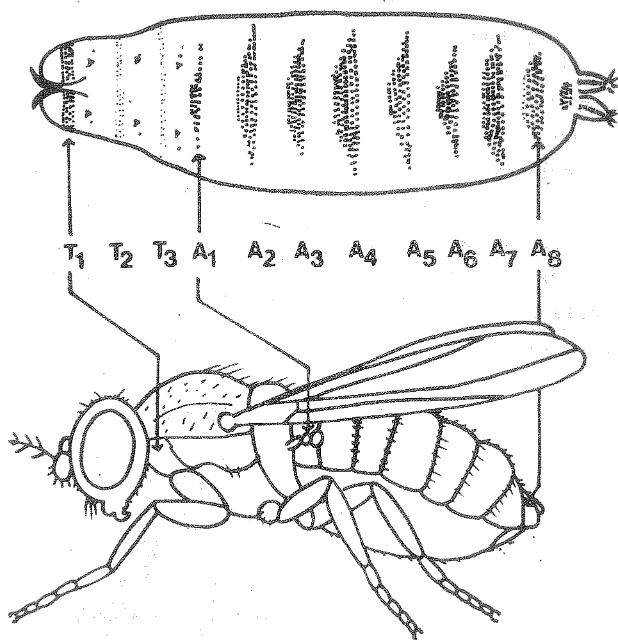

Fig. 1. Diagrammatic representation of body organization in larva and adult of *Drosophila*. Both are made up of a linearly arranged series of repeated units or segments. The three thoracic (T_1 – T_3) and eight abdominal (A_1 – A_8) segments in larva and adult are indicated.

2. Early Drosophila Development

A fertilized female lays an egg that is 0.5 mm long and 0.2 mm wide. Externally, the egg has distinct anterior and posterior poles, dorsal and ventral surfaces. Within 1.5 hours of syngamy the nucleus undergoes nine very rapid and synchronous divisions following which they migrate towards the egg surface. The syncitial embryo at this stage is composed of a single layer of cortically located nuclei of uniform appearance. The only morphologically distinct nuclei at this stage are the "pole cells" located at the posterior pole. These pole cells are precursors of the future germ cells. The cortical nuclei undergo another four rounds of divisions after which (at about three hours of development) the egg membrane furrows in between adjacent nuclei to delimit individual cells. This transforms the syncitial blastoderm into a cellular blastoderm.

In spite of the overt uniformity of the blastoderm cells, they differ in their developmental fates. This was demonstrated by transplantation and cell ablation experiments in which nuclei or cells from one part of the embryo were transplanted to another, or specific nuclei were selectively killed and the resulting patterns examined (Lohs — Schardin *et al* 1979; Hartenstein *et al* 1985). **Nuclei** transplanted before the cellular blastoderm stage assume the fate of cells surrounding their site of transplantation. On the contrary, **blastoderm cells** retain their original fate irrespective of their transplantation site. This made it clear that the fate of a cell was a function of its position on the blastoderm. However, the fate of the progeny of a cell is refined sequentially as new cells are formed. The entire basic body plan is thus established at the cellular blastoderm stage which is subsequently elaborated.

Soon after the blastoderm is formed the process of gastrulation follows. At this stage the identical blastoderm cells begin to show signs of differentiation. Cells along the ventral mid-line invaginate into a ventral furrow. Soon the cephalic and dorsal mid gut invaginations also occur. These furrows form internalized cell pools that eventually give rise to the endoderm and mesoderm. By 6 hours the outer ectoderm, termed the germ band, is fully extended and the first morphological signs of segmentation become visible. The three gnathal, three thoracic and about nine abdominal segments become demarcated by grooves. The grooves however demarcate paraseg-

ments and not segments (see section 5). When the germ band is fully extended, the last parasegment is on the dorsal surface just behind the head. Between 7 and 9 hours, the germ band retracts so that the posterior most parasegment is finally brought to the posterior pole of the embryo. Several other differentiation events occur till the larva hatches out at 24 hours. Ultimately each larval segment gives rise to its corresponding adult segment.

3. The segmented body structure is generated in two steps

The generation and diversification of embryonic segments occurs sequentially in two steps during early development. Initially, the global features of the egg along the anterior-posterior and dorso-ventral axes are decided. This is followed by subdivision of the embryo into the correct number, order and polarity of segments.

To understand how body pattern develops, we can begin by asking some questions such as: How are the primary body axes determined? How is this body axis converted to a segmented situation and how the segments acquire their appropriate identity?

Answers to these questions have been obtained by studying mutations that affect embryonic body pattern. Such mutations are usually lethal at the embryonic stage. The effect of the mutations can be easily studied by looking at cuticle of the dead embryos (see Fig. 2) or by observing embryogenesis. Careful observation and analysis of the mutants can lead to an assessment of the function of the wild type allele. An exhaustive screening of the *Drosophila* genome for all kinds of mutants for body patterning has been conducted by several workers (Nusslein-Volhard and Wieschaus, 1980; Nusslein-Volhard *et al*, 1984; Jurgens *et al*, 1984; Wieschaus *et al*, 1984; Schupbach and Wieschaus, 1986).

In general, mutants affecting embryonic development can be classified into one of the three categories. The first kind (**maternal effect co-ordinate genes**) has a global effect on the embryo and influences almost

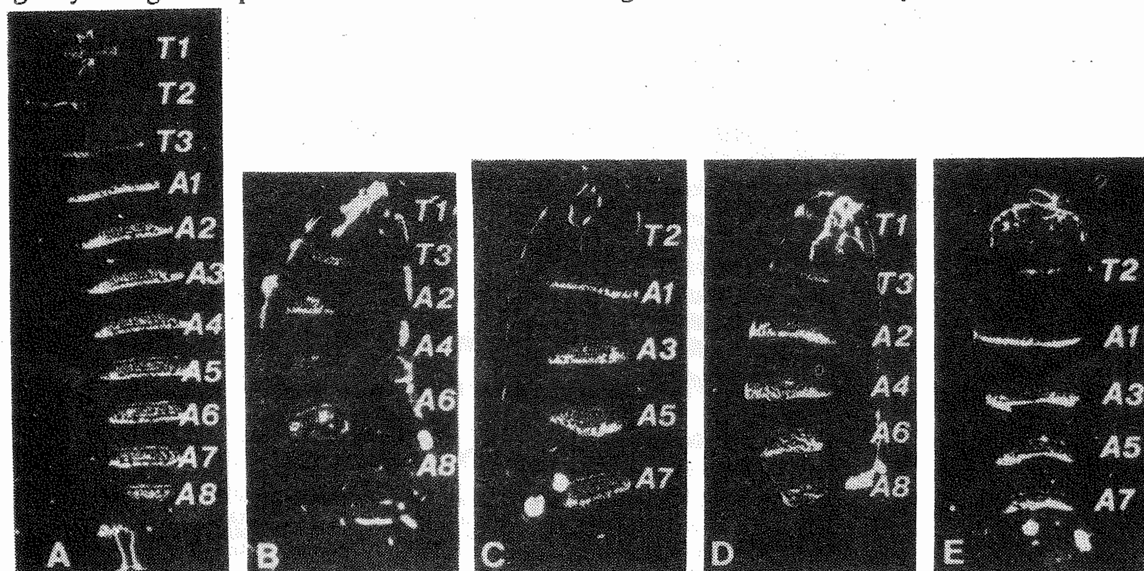

Fig. 2. Cuticular preparations of wild type (A) and some pair-rule mutant (B-E) embryos to demonstrate normal and mutated segmentation patterns. Three thoracic (T1 to T3) and eight abdominal (A1 to A8) denticle bands are seen as bright rows in a fully developed wild type embryo (A). In the pair-rule mutant embryos, alternate bands of denticles are not formed: in the case of *runt* (B) and *fushi tarazu* (C) the odd-numbered abdominal belts and T2 are deleted while in the case of *hairy* (D) and *even-skipped* (E) the even numbered abdominal belts and thoracic belts T1 and T2 are lost (Figure reproduced with permission from Ingham and Gergen, 1988).

every region. The products of such genes are expressed maternally during oogenesis. Very often their products are made in the nurse cells (that surround the growing oocyte within an ovarian follicle) and are exported to the oocyte. They are usually distributed over large areas of the egg cytoplasm in gradients and thereby specify anterior-posterior and dorso-ventral body axes of the embryo during early development (see Section 4).

The second category of genes (segmentation genes) affects either the number or polarity of the body segments (see Fig. 3) without altering the overt polarity of the egg. These genes are expressed after fertilization. Both by genetic and molecular methods it has been shown that the maternal gene products control the activity of these segmentation genes (see Section 5).

The third category of genes (homeotic genes) serves to impart identity to the segments and have no effect on the body axes, segment number or polarity. Mutations in these genes convert one body segment into another (see Section 6). These are controlled by the maternal and segmentation genes. The activities of these three groups of genes follow a cascade: each step controlling the next which elaborates the pattern laid by the previous set of genes.

A major contribution to the understanding of genes affecting early embryonic development was the use of techniques to localize the transcriptional and/or translational products of these genes to specific cells *in situ* during embryonic development. Specific transcripts can be localized in cells by *in situ* hybridization of a labelled cloned probe to RNA in cytological or his-

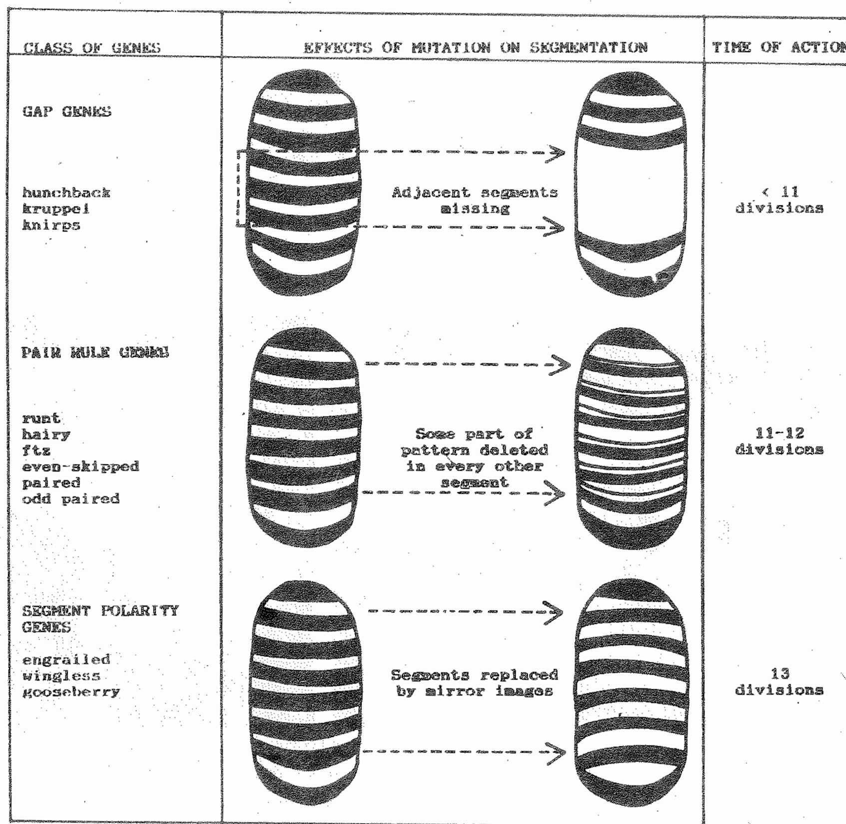

Fig. 3. Diagrammatic representation of effects of mutation in the three classes of segmentation genes on embryonic phenotypes.

tological preparations so that only those cells which contain those specific transcripts show the label (see Fig. 4). Translational products of specific genes can also be localized in cells by immunocytochemical staining techniques in which antibodies to the specific proteins (produced by the gene in question) are used. Thus a combination of genetic (identification of the mutant genes), recombinant DNA (cloning of the identified gene) and molecular cell biological (*in situ* localization of transcripts and/or translational products in cells/tissues) techniques has become a very popular and rewarding approach in such studies.

4. Maternal Genes and the Global Organisation of the Embryo

By the time the egg is laid, the activities of certain maternal genes establish gradients of their products along the antero-posterior and dorso-ventral body axes of future embryo. These maternally acting genes have been divided into three groups (Table 1) depending upon their effects. The genes *bicoid* and *nanos* lay down the earliest protein gradient patterns in the anterior and posterior halves, respectively, while a gradient of the *dorsal* gene product decides the dorso-ventral pattern (see Figs. 5 and 6). The remaining

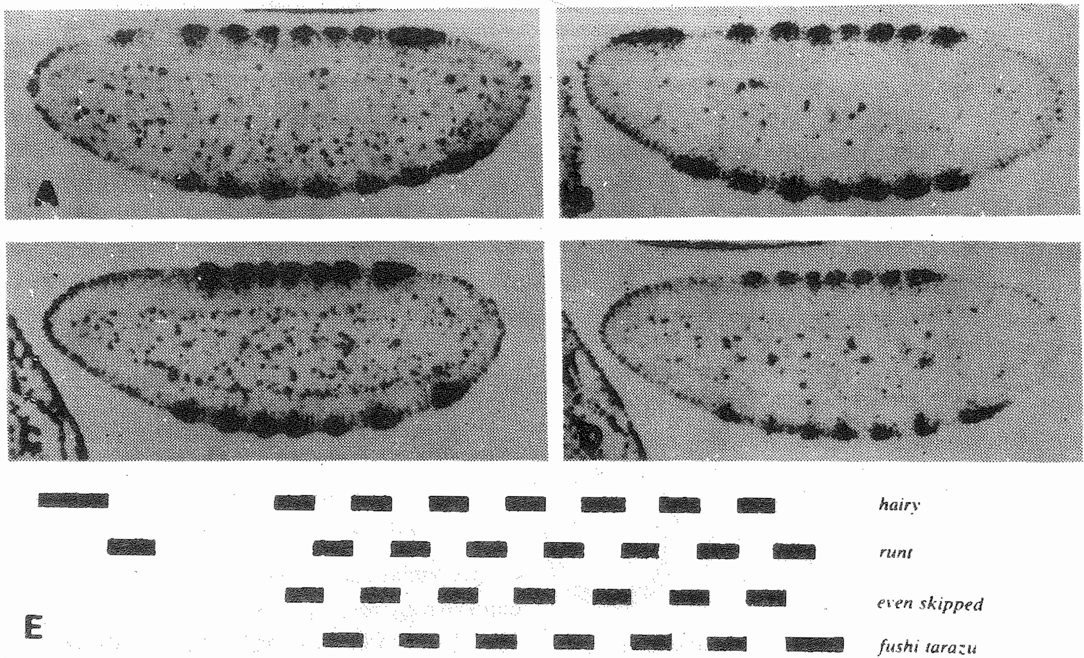

Fig. 4. Expression of different pair-rule genes in spatially distinct sub-set of cells along antero-posterior axis of cellularizing blastoderm embryo of *D. melanogaster* as detected by *in situ* hybridization of radioactively labelled gene probes (A, *runt*, B, *hairy* C, *fushi tarazu* and D, *even skipped*) to cellular RNA in histological (longitudinal) sections of stage 14 (cellularizing blastoderm) embryos: the dense clusters of silver grains, arranged in 7 or 8 stripes, reveal the cells which contain specific pair rule gene transcripts (only the dorsal and ventral margins of otherwise continuous stripes can be seen in these sections of embryos). The relationship of the four transcriptional domains in late stage 14 embryos is shown in E. It may be noted that adjacent subsets of cells (anterior to posterior) express different combinations of pair rule genes; this results from the earlier expression of different gap genes in different regions; the different combinations of pair rule gene expression in turn would activate different sets of segment polarity genes at a later stage (Figure reproduced with permission from Ingham and Gergen, 1988).

genes in the group serve to spatially organize and activate these gradients.

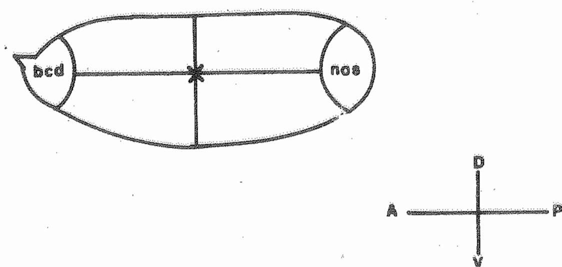

Fig. 5. Diagrammatic representation of the anterior and posterior morphogenic gradients in *Drosophila* egg. By 2.5 hours, the *bcd* protein gets distributed in a gradient from the anterior tip to about 50% egg length. Likewise, the *nanos* protein is also presumed to form a gradient on the posterior end.

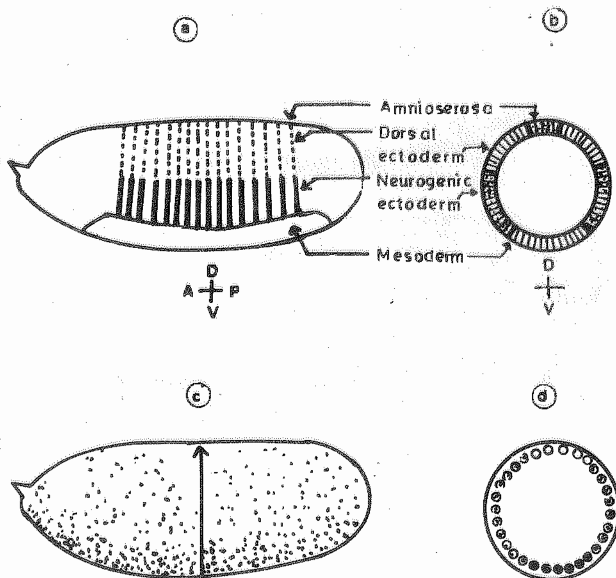

Fig. 6. Dorsal-ventral fate map of the blastoderm of *Drosophila* as seen from side (a) or in a cross section at 50% egg length (b). By the 10th cleavage division, the *dorsal* protein gets intra-nuclearly distributed in a ventro-dorsal gradient: seen from side in c and in a cross section in d.

4.1 The Anterior centre is Organised by a Gradient of the Bicoid Protein

The *bicoid (bcd)* gene was identified by lethal mutations which lead to loss of embryonic head and thoracic structures (Frohnhoffor and Nusslein-Volhard, 1986). Its mRNA is made in nurse cells, exported and localized in the anterior pole of the developing oocyte. After egg deposition, around the time of 7th nuclear division it is translated and the *bicoid* protein diffuses posteriorly to form a concentration gradient over half the egg length (Driever and Nusslein Volhard, 1988; see Figs. 5 and 7) The *swallow* and *exuperantia* genes serve to trap the *bcd* mRNA, maintain its localization and gradient distribution. The *bcd* protein has morphogenic properties. Transplantation of the *bcd* containing cytoplasm to an ectopic site induces head and thorax structure there. This inducing ability is proportional to concentration of the *bcd* protein (Frohnhoffor and Nusslein-Volhard, 1986). It is in fact a concentration dependent transcriptional regulator of segmentation genes (Driever *et al* 1989; Struhl *et al* 1989) The deduced amino acid sequence of *bcd* contains a homeobox (Berleth *et al* 1988; see section 6 for homeobox). Migrating blastoderm nuclei come in contact with different levels of *bcd* protein in the cytoplasm and react by turning on the transcription of the two gap segmentation genes *hunchback (hb)* and *Kruppel (Kr)* around the 10-11th mitotic division. *hb* is expressed in two domains spanning the anterior 50% and posterior 25% of the egg, while *Kr* is expressed in a single band in the centre of the egg. Thus a simple graded pattern of *bcd* protein distribution is transformed into a broadly subdivided embryo by *hb* and *Kr*. (Fig. 7).

4.2 The Posterior Centre is Organised by the Product of Nanos

Proper organization of the posterior centre of the embryo requires activity of at least eleven genes (Table 1). Mutation in any one of them leads to absence of abdominal segments. The *nanos (nos)* gene appears to play the key role of a morphogen and exerts a long range effect over the posterior half. The other genes are involved in export, localization and stabilization of *nanos* gene product.

The *nos* transcript is made in nurse cells and exported to the posterior pole of the oocyte with the help of *Bic D* (Suter *et al*, 1989) The *vasa* product helps to stabilize and activate the *nos* signal (Struhl *et al* 1989).

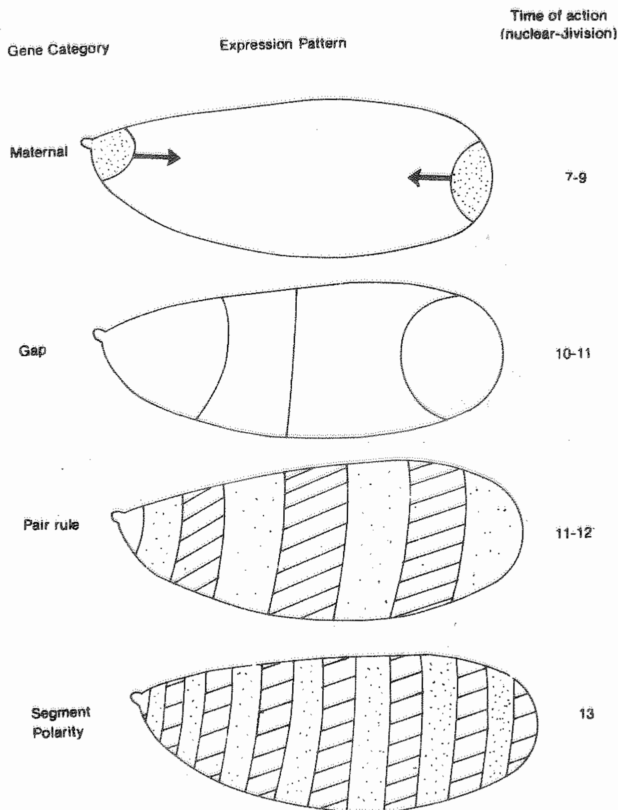

Fig. 7. Sequential activation of genes involved in organization of the 14 parasegments in *Drosophila* embryo: starting with the maternally determined antero-posterior gradients of morphogens, activities of different gap genes demarcate 4 zones which are refined by pair rule genes to identify seven stripes of differently determined nuclei along the antero-posterior axis of embryo; consequential activation of different subsets of segment polarity genes along the antero-posterior axis leads to generation of the 14 parasegments from these 7 stripes.

After egg laying, *nos* is transported from the posterior pole of embryo to a more anterior region probably with the help of *pumilio* and thus establishes a posterior concentration gradient. The precise interaction among the posterior group genes is still to be elucidated.

Table 1. *Genes that control body segement pattern during early embryogenesis in Drosophila*

CLASS	SUB-CLASS	GENES
Maternal	Anterior	bicoid, exuperantia, swallow
	Posterior	nanos, tudor, staufen, vasa, oskar, pumilio, valais, spire, caudal, Bic-C, Bic-D
	Dorso-ventral	dorsal, Toll, easter, snake, pipe, nudel, gastrulation, defective, tube, spatzle, pelle, wind beutel
Zygotic Segmentation	Gap	hunchback, kruppel, knirps
	Pair rule	hairy, runt, even skipped, odd skipped, odd paired, sloppy paired, paired, fushi tarazu
	Polarity	wingless, engrailed, gooseberry, patched, fused, hedgehog, armadillo, cubitus-interruptus
Homeotic	Bithorax complex	antero-bithorax, bithorax, bithoraxoid, post-bithorax, Ultra-bithorax, infra-abdominal2 (iab2), iab3, iab4, iab5, iab6, iab7, iab8
	Antennapaedia complex	Antp, Sexcombs reduced, Deformed, proboscipedia

The *nos* product later activates transcription of the zygotic gap segment gene *knirps* in two domains (on either side of *Kruppel), by* inactivating its repressor (Hulskamp *et al* 1989, Irish *et al* 1989, Struhl *et al* 1989). Thus the maternally deposited gradients of *bcd* and *nos* lead to a subdivision of the embryo into 4 broad subdivisions (Fig. 7).

4.3 Dorso-Ventral Polarity of the Embryo is laid by a Gradient of the Dorsal Gene Product

A fundamental difference between the patterns along the antero-posterior and dorso-ventral axes is that the latter does not have repeated units. The cells along the dorso-ventral axis represent a non repeated series of unique cell types belonging to the ventral mid line, ventro lateral, dorso lateral and dorsal mid line.

Functions of eleven maternal genes are required between the time of fertilization and formation of cel-

lular blastoderm for proper dorso-ventral polarity. Null mutations (mutant alleles which do not make any product) in any of these leads to conversion of ventral into dorsal structures. However, injection of wild types cytoplasm into mutant embryos rescues normal ventral structures (Anderson and Nusslein Volhard, 1984). The products of these genes are therefore required in normal ventral structure differentiation. On the basis of cytoplasmic rescue experiments it was proposed (Anderson *et al* 1985) that interaction among 10 of these genes was responsible for formation of a ventral to dorsal gradient of the *dorsal* gene product (Fig. 6). Cytoplasmic transplantation experiments suggest that the *Toll*+ product decides the ventral point of the axis. Presently available information indicates that the *dorsal* gene represents the last step in the interaction among all the dorsal group genes, and its protein has morphogenic properties (Steward, 1989; Roth *et al, 1989*).

The dorsal mRNA is synthesized in nurse cells, exported to the oocyte and is uniformly distributed in the newly fertilized egg (Steward *et at*, 1988; (Steward, 1987). By the 9th mitotic division of the blastoderm nuclei the mRNA is translated and the protein continues to be uniformly distributed in the cytoplasm. After the 9th division the protein is translocated into nuclei at the ventral side but it continues to remain in the cytoplasm at the dorsal side, thus forming a ventral to dorsal nuclear gradient (Fig. 6, Steward, 1989). The dorsal protein is structurally similar to the eukaryotic transcription factor NF-KB (Leonardo & Baltimore, 1989) and serves to activate transcription of several zygotic genes in a position specific manner along the dorso ventral axis.

5. Segmentation Genes Respond to Maternal Gradients and Subdivide the Embryo into 14 Parasegments in three Steps

We have seen how gradients of maternally produced gene products are established across the embryonic axes around the time of nuclear migration. This continuous graded information is converted by region specific expression of zygotic segmentation genes first into four, then 7 and finally 14 para segments.

As discussed in section 2, the adult fly and mature larva are made up of a linear series of segments. We shall concern ourselves with the three thoracic (T1, T2 and T3) and eight abdominal segments (A1 to A8). The earliest signs of the segmentation process are visible in a 6 hour embryo. The shallow grooves separating each of these early "segments" actually represent the mid points of each larval segment and are called parasegments. Each parasegment consists of the posterior half of a segment and the anterior half of the next segment. For example, the larval segment T1 is formed from parts of parasegment 3 and 4; T2 from parasegment 4 and 5 and so on. There are 14 such parasegments along the length of the embryo.

The generation of parasegments involves about 20 genes. (Table 1) These were identified by mutations which can be classified into three groups (see Fig. 3) on the basis of the size of the segment unit that they affect:

1. **Gap genes** - Mutants in these genes affect several adjacent segments. Major genes in this group are *hunchback, Kruppel* and *knirps.*

2. **Pair rule genes** - Mutants in these genes delete every alternate parasegment. There are two kinds of pair rule mutants affecting either odd or even numbered parasegments. The major pair rule genes are *hairy, runt, fushitarazu, odd paired, even skipped* and *paired.*

3. **Polarity genes** - Mutants in these genes delete parts of the posterior compartment of every segment and replace it with a a mirror image duplicate of the anterior compartment. Some of the polarity genes are *wingless, engrailed* and *gooseberry.*

The gap genes are the first to be transcribed (around 10-11th mitotic division) in response to *bcd* and *nos* gradients. This leads to primary subdivision of the embryo into 4 broad domains. The proteins encoded by them have zinc-finger DNA binding regions (Rosenberg *et al* 1986; Tautz *et al* 1987) and regulate expression of their own and of the pair rule genes which are activated as the next step in segmentation.

The primary pair rule genes *hairy* and *runt* are expressed initially in a uniform manner around the 12th nuclear division. After the 13th division but before cellularization, *runt* and *hairy* expression appears in two complementary series of seven stripes along the embryonic length (Ingham *et al*, 1985; see Fig. 4). This serves as a trigger for the refinement of spatial expression of the next group of pair rule genes *fushi tarazu* and *even skipped*. The *ftz* and *eve* transcripts are made during early blastoderm and gastrula in 7 alternate stripes of 4 cell width. (Hafen *et al* 1984) The *ftz* stripes correspond to even numbered parasegments 4, 6, 8, 10 etc. Mutations in *ftz* and *eve* genes result in loss of even and odd parasegments respectively.

Different pair rule genes are expressed sequentially over a period of thirty minutes in overlapping stripes (see Fig. 4). As a consequence of this, each strip of 4 cells expresses different combinations of pair rule genes. These stripes serve as a new reference point for elaboration within each parasegment by polarity genes. In particular, the *ftz* and *eve* genes encode homeodomain containing proteins that act as transcriptional activators of segment polarity genes *engrailed* and *wingless*.

The *engrailed* transcript accumulates in single cell stripes at the posterior edge of every parasegment (see fig 1, p 178 showing expression of *engrailed* promoter in regions corresponding to the posterior compartment of wing), while *wingless* accumulates at the anterior edge (Ingham *et al*, 1988) to determine the correct anterior and posterior limits of every parasegment.

The segmentation genes thus define the number and polarity of each parasegment in the embryo. The stage is now set for imposing unique identities to each parasegment. This is achieved by the activity of homeotic genes.

6. Homeotic Genes Specify the Identity of Parasegments

Homeotic genes are classically defined by their mutant phenotypes which transform one segment into another. The mutant *bithorax* for example transforms part of the haltere (haltere is the second pair of wings which is normally not developed in dipteran files) into the wing. The homeotic genes fall into two major and complex groups—the *Antennapaedia* complex (Ant-C) and *Bithorax* complex (Bx-C), each containing several complementation groups (functionally distinct genes). These genes are activated in response to gap, pair rule and some maternal regulatory genes. The Bx-C genes define identity of body segments beginning from posterior T2 to A8 and genes of the Ant-C define segments anterior to T2 (see Fig. 8).

Each of the genes of the Bx-C defines one parasegment. The left to right order of genes on the genetic map of Bx-C corresponds to the order of the segments (T2 to A8) that they affect. Thus, moving from left to the right of the Bx-C, each recessive mutant usually affects segments T2 down the fly to A8. A working model for the mechanism of Bx-C function supposes that every segment sequentially requires an additional Bx-C gene function over its previous one. The A8 segment therefore requires of expression all the Bx-C genes in contrast to T2 (anterior) which requires none of them (Lewis. 1978; Fig. 9). In other words, anterior cells in T2 acquire their identity because none of the Bx-C genes express in those while the cells in A8 know that they are A8 cells due to expression of all the Bx-C genes in them.

The cluster of genes of the Ant-C complex also show colinearity between gene order and their position of expression in the body (see Fig. (8). Among mutants in this complex locus are alleles which change antenna into legs or second and third leg into first leg (Scott, 1987).

The transcription patterns of the Bx-C and Ant-C genes correspond to the positions of segments affected by their null mutants. It appears from this that cells learn their identities from the activities of homeotic genes within them (Akam, 1983; Levine *et al*, 1984). The homeotic genes can therefore be regarded as regulators of development within and between segments.

One unifying theme among homeotic (and some segmentation) genes is that they contain a 180 bp sequence of DNA called the homeobox which encodes a highly conserved 60 amino acid sequence, the homeodomain (Levine et al, 1983). This is a DNA binding domain and functions to regulate the transcription of the other genes that lead to segment specific differentiation.

Conclusions

The general principle that emerges from the above is that there are three groups of genes that control body

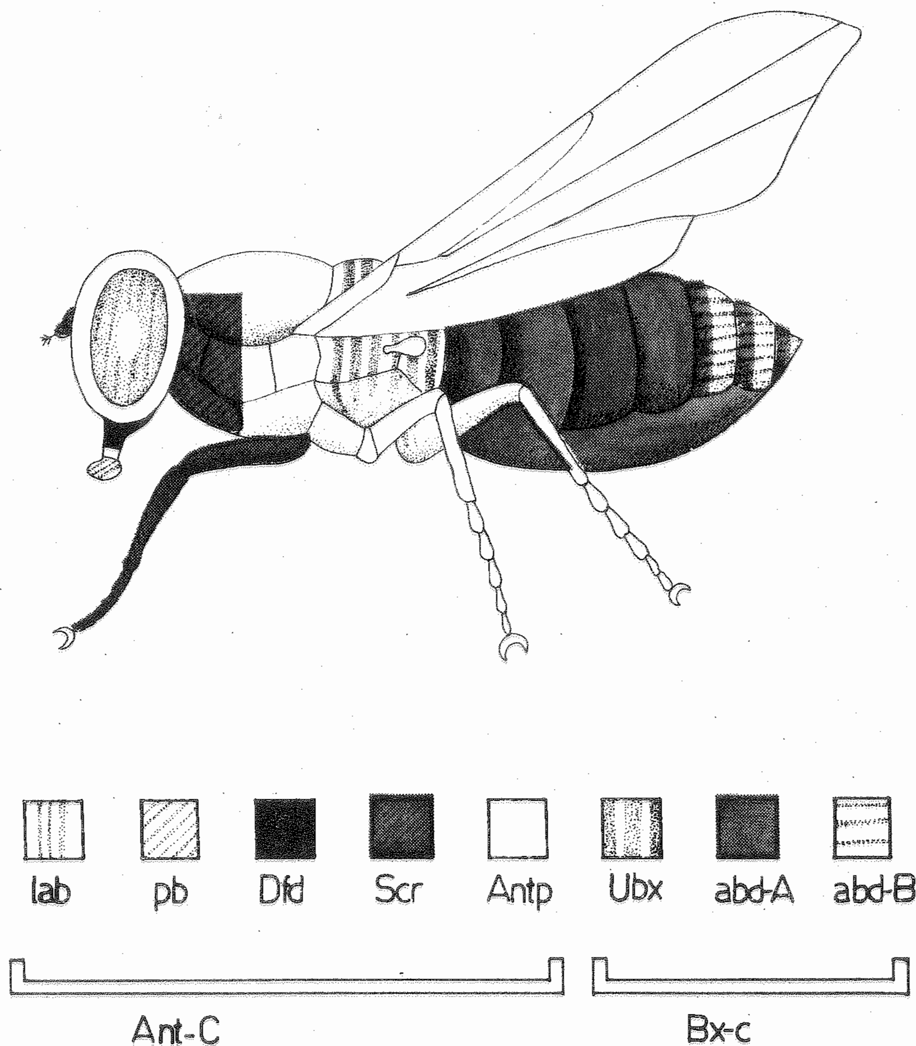

Fig. 8. Correlation of the functional domains in the adult fly with genetic map of the homeotic genes of the *Antennapedia (Ant-C)* and *Bithorax (Bx-C)* complexes. The order of individual genes on the genetic map of each complex locus is strictly colinear with the metameric domains they specify during development. The *Ant-C* complex includes *labial (lab), proboscipedia (pb), Deformed (Dfd), Sex-combs reduced (Scr)* and *Antennapedia (Antp)* genes while the Bx-C complex includes three protein-coding regions, viz., *Ultrabithorax (Ubx), Abdominal-A (Abd-A)* and *Abdominal-B (Abd-B)*. The *Ubx, Abd-A* and *Abd-B* are further subdivided into several mutational sites on the basis of effects of each mutation (see Fig. 9). While the *Ant-C* region spans about 103 kilobases (kb) DNA, the *Bx-C* region is more than 300kb long. (Figure redrawn after Dessain and McGinnis, 1991).

segmentation during early development. It is also clear that specification of a given body segment cannot be correlated with a single segmentation gene. Actually each of the segmentation genes is expressed in cells which have very different fates. Thus a question that arises is : how do these genes really determine specific fates of cells according to their locations in the embryo? The answer perhaps lies in the fact that the combination of segmentation genes that is sequentially expressed in a given cell type is unique to that cell type. Since all of the segmentation genes appear to code for transcription factors (proteins that bind to specific gene promoters to regulate their expression), specific combination of these transcription factors that thus becomes available in a cell activates and/or represses a specific set of genes in a cascade. This cascade regulates other target genes to make specific structural proteins which drive the cell along a specific developmental pathway.

Analogous studies on widely unrelated organisms such as mice, frogs, nematode worm (*Cenorhabditis elegans*) and yeast are revealing that these organisms also follow similar rules of development. Many of the segmentation and homeotic genes of *Drosophila* have been shown to have their counterparts (homologous genes) in diverse organisms and to have similar uses in development. Future prospects for solving mysteries

LARVAL SEGMENTS	abx	bx	pbx bxd	iab2	iab3	iab4	iab5	iab6	iab7	iab8
	Ubx			Abd-A			Abd-B			
T_1										
T_2	+									
T_3	+	+								
A_1	+	+	+							
A_2	+	+	+	+						
A_3	+	+	+	+	+					
A_4	+	+	+	+	+	+				
A_5	+	+	+	+	+	+	+			
A_6	+	+	+	+	+	+	+	+		
A_7	+	+	+	+	+	+	+	+	+	
A_8	+	+	+	+	+	+	+	+	+	+

Fig. 9. Model for position specific activation of successive loci in the *Bx-C* region: the *Bx-C* region defines different thoracic and abdominal segments by recruiting activity of successive loci in the region to distinguish each segment from the anterior segment. A + in the diagram indicates requirement of activity of the given locus in a segment.

of body organisation in a wide range of organisms along the lines of the lessons learnt from fruit fly development are therefore excellent. An understanding of the genetic regulation during early embryonic development has also made it clear that such cascades of gene regulation (one set of genes regulating the next set which in turn regulates another set and so on) are not unique to early development but operate all the time in every cell. This interaction of genes within and between cells is the key to individuality of every cell in a body. Interestingly, it is this individuality of every cell that generates more such cascades and results in a wholesome coordinated body organization so characteristic of living systems.

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If an engineer were asked, starting from scratch, to manufacture a frog, it seems unlikely that he would first design such a swimming precursor as a tadpole and transform it later to a land animal. If he were asked to build a human baby, there is little chance that he would go through an embryonic stage with the gill slits and the complicated pattern of circulation that persists up to the adult stage of fishes.

In contrast to the engineer, evolution does not produce innovations from scratch. It works on what already exists, either transforming a system to give it a new function or combining several systems to produce a more complex one. The way evolution proceeds has no analogy with any aspect of human behaviour. If one wanted to use a comparison, however, one would have to say that this process resembles, not engineering, but tinkering, *bricolage*, as it is called in French. While the engineer's work relies on his having the raw materials and the tools that exactly fit his project, the tinkerer manages with odds and ends. Often without even knowing what he is going to produce, he uses whatever he finds around him, old carboard, pieces of string, fragments of wood or metal, to make some kind of workable object. What the tinkerer ultimately produces is often related to no special project. It merely results from a series of contingent events, from all the opportunities he has had to enrich his stocks with leftovers. When evolution turns a leg into a wing or a part of jaw into a piece of ear, it behaves somewhat like a tinkerer who makes a fan out of an old car wheel or a book case out of an old table. In a way, evolution proceeds like a tinkerer who, during millions of years, has slowly modified his products, retouching, cutting, lengthening, using all opportunities to transform and create.

(Source: *Molecular tinkering in evolution* by Francois Jacob)