The Role of Compartmentalization in the Activation of Particular Control Genes and in the Generation of Proximo-Distal Positional Information in Appendages

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SYNOPSIS. A mechanism is proposed for the activation of particular genes during interpretation of positional information and during sequential addition of new structures during outgrowth. The primary event is assumed to be an alternation between two states. The alternation of anterior-posterior-anterior compartments in insects or bone-joint-bone in the chicken wing is assumed to be a trace of this primary subdivision into two alternative states. Each (or each second) transition from one state to the other causes a switch from one structure-controlling gene to the next. This enables a counting of alternations on the DNA-level and a high resolution in the corresponding activation of control genes. The model explains the formation of compartments and segmental specification in perfect register. The elements of the bithorax gene complex become understandable assuming this mechanism.

It is shown further that such a "compartmentalization" can be used for the reproducible generation of subpatterns for the finer subdivision of a developing embryo. By "cooperation of compartments," a cone-shaped morphogen distribution can be generated, accounting, e.g., for the circular arrangement of structures in the fate map of the leg disk of Drosophila. The most distal structures are formed at the intersection of compartments and distal transformation occurs whenever cells of all three or four major compartments are close to each other.

INTRODUCTION

Experimental evidence suggests that not every structure of a developing organism is determined independently but rather that sequences of structures are under a common control. A classical model for this involves the assumption of a graded distribution of a morphogenetic substance providing positional information (Wolpert, 1969, 1971). The cells of a field are thus exposed to differing morphogen concentrations which are responsible for the activation of different developmental pathways, each corresponding to the local concentration experienced by a cell. This interpretation of positional information converts the morphogen gradient into a sequence of structures. This concept has been especially successful in explaining experimentally induced pattern alterations in the digits of vertebrate limbs (Tickle et al., 1975; Slack, 1977a, b) and in early insect development (Sander, 1976; Meinhardt, 1977). The analysis of segment formation after transverse ligation of insect legs has provided an important indication as to how the cells interpret positional information. They do not measure it all at once but rather are changed stepwise from lower, more anterior (or proximal) to more posterior (or distal) determinations until the determination corresponds to the local morphogen concentration (Meinhardt, 1977, 1978a).

In insects as well as in vertebrate limbs, two processes are superimposed: The first consists of the formation of a periodic structure. In the vertebrate limb, areas of presumptive digits and areas of programmed cell death alternate. In insects, the periodic structure consists of segments and segment borders. The second of the two superimposed processes is the determination of the specific structure to be formed. The digits as well as the insect segments are different from one another. We do not know precisely what the developmental steps are which lead to segmentation, but among the earliest developmental decisions is, at least in the thoracic segments, the subdivision of the blastoderm into alternating regions of anterior (A) and posterior (P) specification. These compart-

ments (Garcia-Bellido et al., 1973, 1976; Steiner, 1976) are arranged like zebra stripes. Each segment consists of an anterior and a posterior band. Since both processes, the generation of periodic structure and the particular specification of its elements are in register, it is tempting to assume that the primary event is a discontinuous specification. A segment border or a zone of cell death is formed consequently at the location of a transition from one specification to the next. A molecular model which is able to activate particular control genes under the influence of a morphogen and to form thereafter subpatterns within cells of the same specification has already been proposed (Meinhardt, 1978b, 1979). However, it is possible as well that the formation of a simple periodic structure is the primary event and that specification is governed, for instance, by a mechanism, counting the alternations. Mutations are known in Drosophila which imply that it is the latter mechanism which is utilized. A fly carrying the mutations bithorax (bx) and postbithorax (pbx) forms a meso- instead of a metathorax and has a second pair of wings instead of halteres (Lewis, 1963, 1964, 1978; see Fig. 3). It is important to note that two mesothoracic segments are formed and not a single but very large segment, implying that the formation of a segment boundary does not require the transition from one determination to the next. On the other hand, a fly with a Cbx-mutation forms metathoracic structures in the posterior mesothorax. Meso- and metathoracic structures are formed in one and the same segment, signifying that a transition from one specificity to the next does not induce a segment border.

Reaction-diffusion mechanisms can lead to spatial periodic structures which are stable in time as well as to oscillating systems (see Meinhardt and Gierer, 1974). In the present paper, I would like to propose a mechanism for the interpretation of positional information in which the primary step is a conversion of cells oscillating between two alternative states into a stable spatial periodic arrangement of these two states. The early subdivision of the thoracic segments into anterior and posterior compartments appears as a trace of this primary alternation. Each (or each second) transition from one state to the other is assumed to cause the transition to a subsequent control gene. This leads to a periodic structure—the compartments—and to a sequential structure—the specific determinations. Both are in perfect register. After the description of the necessary ingredients for such a mechanism, I show that the mutants of the bithorax complex are simply understood using this assumption. It will become evident why most of the mutants affect only one half of a segment. In a second part of the paper, a mechanism for the generation of a subpattern is described in which compartmentalization plays a decisive role.

The Pendulum-Escapement Model

The basic idea can be illustrated by an analogy. Imagine a grandfather clock. The weights are at a certain level (corresponding to the local morphogen concentration). They bring a pendulum into movement which alternates between two extreme positions. The escapement mechanism allows the pointer to advance one unit after each change from one extreme to the other. As the clock runs down, the number of left-right alternations of the pendulum and hence the final position of the pointer is a measure for the original level of the weights (level of morphogen concentration). In terms of the mechanism for the interpretation of positional information, we will assume that, under the influence of the morphogen, the cell alternates between two states, to be called A (anterior) and P (posterior) and that the total number of alternations corresponds to the local morphogen gradient. Simultaneously with each P → A transition the cells switch from one specification i to the next, i + 1 (i = 0, 1, 2 ... n). A particular state of a cell can be characterized by its A-P state and its specification, for instance, 1A, 1P, 2A and so on.

In Figure 1, different stages in the process of interpretation are shown. It can be seen that the cells exposed to a low morphogen concentration (e.g., the head or
The interpretation of positional information according to the pendulum-escapement model. (a) The antero-posterior morphogen gradient, providing positional information. (b) The time-sequence of the compartmentalization. Originally (time 0) the cells are in P-state (X). Those cells exposed to a threshold morphogen concentration switch to the A-state (:) and simultaneously from gene 0 to gene 1. Those A cells without P-neighbors switch back to the P-state, and so on. (c, d) The final result is a subdivision of the egg into anterior (:) and posterior (X) compartments (c) and in accord with that, the activation of a sequence of control genes (d).

The proximal leg structures) obtain their final determination earlier, after a few alternations. The graded morphogen concentration becomes converted into the alternating A-P-sequence and in the sequence of structures 0, 1, ... n. Both patterns are necessarily in register.

The following elements are required for the realization of the model.

(i) The cells can be in one of two states (A or P). The transition from at least one of these states to the other, for instance P → A, requires a threshold morphogen concentration. The alternative transition (A → P) can be an autonomous process like the swinging back of a pendulum.

(ii) The advancement from one specification, that means from one structure-controlling gene activity to the next (i → i + 1), proceeds under the influence of such a transition, e.g., P → A.

THE OSCILLATION BETWEEN A AND P AND THE GENERATION OF STABLE A-P-STIPES

A periodic pattern in space of two alternative states can be achieved by the mutual activation of two states locally excluding each other (Meinhardt and Gierer, 1980).

Let us assume two states, A and P. Each helps the other and, as in symbiosis, both states are dependent on this mutual, long-ranging help. However, both states cannot coexist at a particular location. This necessitates that both structures are formed in close proximity to one another. A stripe-like pattern is especially favored since, in this case, the long common boundary regions enable an effective mutual stabilization. Several molecular realizations are possible. For instance, the mutually exclusive states A and P can result from the autocatalysis of the substances A and P which compete via a common repressor. The mutual help could be realized by diffusible molecules which are produced under the control of A or P and required by the other. An alternative mechanism for the mutual help could be a long ranging self-inhibition, since, due to the competition of the feedback loops with each other, a disadvantage for one of the loops is equivalent to a support for the other (see Meinhardt and Gierer, 1980).

While A and P stabilize each other in the region of a common boundary, it is a property of such an interaction that a group of cells consisting of one type only (A or P) can oscillate back and forth between the two possible states. If, for instance, all cells
are in state A, the state P gets an enormous help while the state A is not supported. After a certain time, the cells switch from A to P. Later, the cells switch back to A for the same reason.

This spatially homogeneous oscillating system would be converted into a pattern which is stable in time if, at any location, an A-P border has been formed. Imagine a linear array of cells, all in the state A, only the leftmost cells in state P. The cells close to the A-P boundary are mutually stabilized while the A-cells at a distance switch to P generating a second A-P-border. This mechanism will continue until the total area is subdivided into a spatial periodic A-P pattern. As the process progresses, the region of a stable spatially alternating A-P pattern will be enlarged at the expense of the spatially homogeneous cells oscillating between A and P in time. The borderline between the stable and oscillating cells moves over the field in a wave-like manner.

The model as developed so far has some similarities with a model for the segmentation of somites proposed by Cooke and Zeemann (1976) in which an oscillator gates a wave front. In the model I propose, the oscillator (alternating between A and P), the wave front, (between stable and oscillating cells) as well as the spatial periodic pattern (of A and P), result from one and the same mechanism. By an appropriate control of the size of the A and P areas, the size of the somites can be adapted to the total size of the embryo. This can be achieved either by control of a low constitutive level of A and P productions (details will be discussed elsewhere) or by the influence of a morphogen gradient, as discussed below.

**The Influence of the Morphogen on the P-A Transition**

As mentioned, the results of many experiments can be successfully described by a model which characterizes early insect development as being under the influence of a morphogen gradient. If it is not the primary specification but rather the formation of the periodic structures which is under control of the morphogen—as postulated in this paper—then either the A → P or the P → A transition or both must be under the control of the morphogen. In the following discussion, we will assume that the P → A transition requires a threshold concentration while the A → P transition is an autonomous process. Let us assume that all cells are originally in the gene-0, P-state (0P). Only those cells which are exposed to a sufficient morphogen concentration will switch to A. Since it is a P → A transition, the cells switch from specification 0 (corresponding, for instance, to extraembryonal development in insects or to the anterior necrotic zone in digit formation) to the state 1. The 0P and 1A cells stabilize each other, while cells further distant switch from 1A to 1P as described above. If the necessary morphogen threshold remains unchanged, a periodic structure would be formed as described above since the next 1P → 2A transition would take place in a region of even higher morphogen concentration. It is conceivable, however, that a certain increase in the next P-A threshold is associated with the 0 → 1 transition. If this were so, a definite increment in the morphogen concentration would be required and the steepness of the gradient would determine the length of a segment.

**How to Create Stable States and How to Advance from One State to the Next Under the Influence of a P → A Transition**

A particular state of determination can be stable over many cell generations. Such "long term memory" can be achieved if a gene controlling a particular structure feeds back on its own activity. The selection of one out of several alternative genes is enforced if autocatalytically activated genes compete in their activity via a common repressor (Meinhardt, 1978b) as has been mentioned already for the generation of the A and P states. A P → A transition can induce a transition from one specification (particular feedback loop) to the next by the following interaction: In the P-state of each particular specification, a substance is produced which activates the next following feedback loop, but the ac-
tion of this "proceed"-substance is blocked. Only after the switch into an A-state can the transition be executed since sufficient "proceed" molecules are still available and their action is no longer blocked. The specification can advance only one unit since in the A-state, no "proceed"-molecules for the next transition are synthesized and therefore, an A → P transition is without effect. The situation may be compared to a sluice which can be at rest at two states: either the lower gate is open and the upper is closed or vice versa. The passage of a ship is prepared by its entrance into the sluice. For the completion of the passage, the sluice has to be switched from one state into the other.

Figure 1 shows a computer simulation of the mechanism proposed demonstrating that it is feasible and free of internal contradictions.

**Modifications Required for a Progress Zone Type of Pattern Formation**

The model has been developed for a morphogenetic field, controlled by a morphogen gradient and with a geometry which remains unchanged during the interpretation of the positional information. However, the mechanism is easily adapted to a system which has a marginal zone of growth, such as the progress zone in the chicken wing bud (Summerbell et al., 1973). In terms of the model, the primary subdivision would not be humerus, ulna, etc. with a joint formed later on between two different specifications but the initial step would be the formation of a periodic structure, e.g., bone, joint, bone, joint ... and with each switch from one state to the alternative a new control gene becomes activated, leading to a sequence bone 1, joint 1, bone 2, ... During outgrowth, whenever an area of the one "compartmental" specification (called again A or P) becomes large enough, the support for the other (P or A) becomes so dominating that a transition occurs. During outgrowth the cells at the proliferation zone switch between A and P after a certain number of cell proliferations. As discussed above, with each or with each second (P → A)

![Diagram](image)
transition, a switch from one specification to the next can be accomplished (Fig. 2). New structures are added during outgrowth and an ordered sequence of structures is formed without recourse to a morphogen gradient. With this mechanism, the segmentation by interpretation of positional information and by a progress zone becomes so similar that combination of both mechanisms can be envisaged in which some segments are formed by interpretation and the remaining segments by marginal growth. In some insect species, the abdominal segments are formed by a sprouting out (see Sander, 1976).

**Comparison with the Alleles of the Bithorax Complex**

Mutations in the bithorax complex (BX-C, Lewis, 1964, 1978) cause homeotic transformations of the metathorax (MT) segment into mesothorax (MS) or abdominal (AB) specifications and vice versa. Most of these mutants affect either the anterior or posterior compartment. I would suggest that the BX-C contains the control genes for the activation of the MT-pathway under the influence of the P-A-P transitions. If one or several of these control genes are mutated, the switch from MS to MT or MT to AB1 (first abdominal specification) no longer occurs at the correct P → A transition. Figure 3 shows the arrangement of these genes on the third chromosome. Hayes et al. (1979) have proposed that the genes are transcribed from an operator region in the *Ubx* region and that the direction of transcription depends on the compartmental specification of the particular cell. It is to the left (proximally) in the anterior compartment thus providing for the transcription of *bx*<sup>+</sup> and *Cb*<sup>+</sup>; while in the posterior compartment it is to the right, and *bxd*<sup>+</sup> and *pb*<sup>+</sup> are tran-
scribed. In the following discussion, I will follow this proposal. The observed mutations and transformations they cause can be correlated with the expected elements of the escapement model as follows.

*Contrabithorax* (*Cbx*). The posterior MS is transformed into MT specification. The posterior portion of the wing becomes thus a haltere. Model: it is expected that a molecule responsible for the MS → MT transition is produced in the posterior MS but that this transition is blocked by a “posterior (P-) block.” A non-functional block would lead to an MS → MT transition prematurely in the posterior MS-segment—which corresponds to the *Cbx*-phenotype. The *Cbx*+ region is therefore assumed to be the binding site of a molecule produced in a posterior compartment, for instance, the molecule P discussed above which blocks the transcription of the gene bx+ by its binding and therewith the MS → MT transition. In agreement with the model, *Cbx* is a dominant mutation since it is sufficient that the P-block is non-functional on one chromosome to allow premature bx+ transcription.

*bithorax* (*bx*). The anterior MT segment is transformed into an anterior MS. Model: with the P(MS) → A transition a switch from MS to MT specification should occur. One possibility for its realization would be a repression of the MS-pathway and/or of the MS-feedback loop by an MS repressor. The bx+ gene is assumed to be the coding site for that repressor. After a P(MS) → A transition, no P molecules are present, the Cbx+ region provides no longer a block for the bx+ transcription, the repressor of the MS pathway is produced and the MS → MT transition is accomplished, along with the correct P → A transition.

*postbithorax* (*pxb*). MS structures are formed in the posterior MT segment; the posterior portion of the haltere becomes a posterior wing. Model: After an A(MT) → P transition, the Cbx-region is blocked again by P molecules and only the right part of the BX-C can be transcribed. The MS-repressor coding site at bx+ would be transcribed no longer. A second MS-repressor coding site is required on a chromosomal site which is transcribed in the posterior compartment. The pxb-region is assumed to be this second MS-repressor coding site. If mutated, MS-structures are formed in the posterior MT-segment.

This scheme is able to account for a strange behaviour of the double mutant *Cbx pxb*. As a rule, the effects of the mutations are additive. For instance bx pxb causes MS structures in the anterior as well as in the posterior compartment of the MT segment. However, a fly with *Cbx pxb* genotype has a pure *Cbx* phenotype, in other words it does not matter whether pxb is mutated or not. According to the model, a mutated *Cbx* locus leads to a constitutive MS-repressor production in the MT-region independent of the compartmental specification as now the bx+ gene is accessible to transcription even in the posterior compartment due to the failure of the block at the *Cbx* location. Therefore, whether the second MS-repressor coding site at *pxb* is functional or not is without influence. The MS pathway is then anyway repressed in the MT segment. This double mutation shows further that bx+ is not a “selector gene” (Garcia-Bellido, 1975) activating specifically the anterior MT pathway. The bx transcription in the posterior MT compartment due to a *Cbx* mutation leads there correctly to an MT pathway despite the mutated *pxb* locus.

*bithoraxoid* (*bxd*). The first abdominal segment (AB1) is transformed into thoracic structures. More precisely, the anterior part acquires MT, the posterior part MS specifications. In addition, the pxb+-gene appears to be non-functional since an MT → MS transformation also occurs in the posterior MT-segment. Model: In the posterior MT-segment, the transition to the next specification has to be prepared. Genes necessary for the different abdominal specifications are located at the right (distal) side of the pxb-gene. We assume that the transcription of AB1-gene is initiated from the posterior *Ubx* operator but blocked (a second posterior block) as long as the system is in the posterior MT stage. AB1 structures are formed only after the next P-A transition. As mentioned, the stabilization of a particular determined state requires a feedback of a control gene
on its own activity. We expect that the bxd+ gene is involved in a Ubx+-bxd+ loop. Therefore, if bxd is mutated, the posterior MT-control loop cannot be activated. This has two consequences. On one hand, the pbx-gene is no longer transcribed and MS-structures are formed in the posterior MT segment. Secondly, the genes necessary to form abdominal structures cannot be activated with the next P-A transition and thoracic structures are formed in the first abdominal segment. As mentioned, MT structures are formed in the anterior AB1 segment and MS-structures are formed in the posterior AB1 segment. After the P(MT-segment) → A(AB1-segment) transition in a bxd fly, the Cbx+-bx+ region is no longer blocked, and the MS-repressor at the bx+ site can be made. Therefore, the anterior part of AB1 is of MT specification. However, in the posterior AB1 segment, the bx-region is blocked again at Cbx, pbx still cannot be transcribed and therefore MS-structures are formed, similar to the posterior MT segment. The model can therefore account for the peculiar MT-MS heterogeneity in the bxd-transformed AB1 segment.

Hyperabdominal (Hab). MT and AB1 segment obtains AB2 specification. Halteres and MT-legs are absent. Model: Hab represents the expected next posterior block for the MT → AB transition, Hab is analogous to Cbx in the MS → MT transition. It represses abdominal control genes from being transcribed from an operator (the Ubx+-bxd+ loop) which becomes activated in the posterior MT segment. A failure of this block would lead to AB structures in the (posterior) MT segment. The MS-segment is not affected because Ubx, and therewith the AB-genes, are first activated in the MT segment. It is not yet clear why AB2 and not AB1 structures are formed in the MT segment.

If, due to a chromosomal deletion, the BX-C is completely absent, the MT and AB1–AB7 segments receive MS specificity. In terms of the model, if the chain of the sequential inductions is interrupted at one element, the following genes in the sequence can be activated no longer. This does not necessarily mean that the BX-C complex is active in the abdominal segments as well. Rather the activation of the BX-C is a necessary but transient step in the activation of abdominal specificities.

The number of segments is not affected by deletion of the BX-C complex. This is remarkable and indicates that the counting of segments is not coupled to the steps in the specification process. The number of segments is normal although almost all posterior segments form MS-structures only. This indicates that during normal development the formation of segments does not come to a rest because, for instance, the last abdominal specification is reached. Giving a segment a name and a number are two different processes. The thresholds for the P-A-transitions must be controlled by the numbering, not by the specification process. On the other hand, we know from the reduced number of segments in “Double-Abdomen” insects (Kalthoff and Sander, 1968; Nüsslein-Volhard, 1977) that the number of segments is coupled to the system of positional information (Meinhardt, 1977).

The model also describes the cis-trans effects of double mutations observed by Lewis (1964). If a Ubx− mutation is located on one chromosome and a bx− on the other chromosome, the operator would be non-functional on the one chromosome and the MS repressor coding site on the other. No MS-repressor can be produced from either and bx-phenotype is expected. In cis, one chromosome is intact and wild-type-phenotype is expected. Cbx in combination with Ubx or bx in trans-position shows the normal dominant behaviour of Cbx since the Ubx+ and bx+, the operator and MS-repressor coding site, on the Cbx-chromosome are not affected. In cis, despite the missing P-block (Cbx), the phenotype is almost wildtype since, either the MS-repressor-coding site (bx) or the operator site (Ubx) is mutated on the Cbx− chromosome and hence no MS-repressor can be prematurely produced. Since transcription proceeds from Ubx either in the bx or in the pbx direction, no cis-trans-effects are expected between combinations of bx or Cbx on one hand and of bx or pbx on the other. A bxd and pbx-mutation
on the same chromosome leaves the other chromosome intact (phenotypic wildtype) while, when located on different chromosomes, the $Ubx$-$bx^d$ loop can be activated only on the chromosome carrying the $bx^d$ gene. But if $pbx$ is mutated on this $bx^d$ chromosome, $pbx^-$ phenotype is expected—as observed.

**Open Questions in the BX-C Assignment**

The model describes quite successfully the general function of the elements of the BX-C, the coincidence of P $\rightarrow$ A transitions and the change in the determination, the phenotype of double mutants, the cis-trans-behaviours of double mutations and whether a mutation is dominant or not. However, some questions remain open or are difficult to resolve on the basis of the existing experiments.

The assignment of $bx^+$ as the MS repressor coding site and part of the $Ubx^+$ as anterior operator is not unequivocal; it can be the other way around also. In the latter case, in A the transcription would start at $bx$ and proceed in the same direction as in the $Ubx^+$-$bx^d$ region. Further, what is the reason that an A $\rightarrow$ P transition in the MS-segment does not lead directly to the activation of the posterior branch of the BX-C genes ($Ubx^+$, $bx^d$, $pbx^+$)? A blocking side ($Cbx$) is known only for the anterior branch ($Ubx^+$, $bx^+$). Indeed there seems to be some instability in segmental transformation connected with an A $\rightarrow$ P transition. Parts of the first leg disk (prothorax) frequently show transdetermination (Strub, 1977b; Karlsson, 1979) into distal wing structures, that is an MS-specification. Distal transformation is presumably connected with a respecification of some A cells into P-cells (see below). It is possible that the activation of the BX-C complex can proceed only via the anterior branch, controlled by $Cbx$. Another possibility would be that the positional information still plays a role for an MS $\rightarrow$ MT transition. In such a case, the role of the compartments would be more to increase (in P) or to lower (in A) the threshold for a switch from one determination to the next. This would also explain why a P $\rightarrow$ A transition in an isolated regenerating disk seems usually not connected with a segmental transformation (Tiong et al., 1977; Adler, 1978).

It is remarkable that many segmental transformations are confined to distal structures only (see Garcia-Bellido, 1977). An example is Antennapedia. As will be shown below, distal structures are necessarily formed close to the A-P compartment border where both states necessary for a transition are in a close neighborhood.

**Cooperation of Compartments for the Generation of Positional Information**

The primary gradient can cause, as has been discussed above, the subdivision of the insect embryo into segments and compartments. By this process, for instance, the segment which has to bear the first pair of legs can be specified, but the fine structure of these legs cannot result from an even more accurate interpretation of the primary gradient. Secondary gradients would be required. Like the whole insect, an insect leg is subdivided into segments. The fate map of a leg disk shows an arrangement in rings: The distal structures are layed down in the center, the more proximal structures in the outer rings (Schubiger, 1968). A morphogen distribution appropriate for the generation of this map would be a cone-shaped distribution, the highest concentration would cause the most distal structures, the 5th tarsal segment and claws in the center while at the marginal areas, at the low concentrations, thoracic structures and coxa are determined. The question is how to generate such a cone-shaped distribution? I have proposed the following mechanism (Meinhardt, 1980): A cooperation of the major compartments is required for the synthesis of the morphogen. Hence, the synthesis takes place only at locations where cells of all compartmental specifications are in close contact with one another. The intersection of the compartment borders becomes therefore the source region of the morphogen. The gradient is formed by this local production,
diffusion and decay. The cells respond to it in the same step-wise unidirectional manner described above. In agreement with this hypothesis, the most distal structures, for instance, the wing tip or the claws of a leg, are formed at the intersections of the compartments (García-Bellido et al., 1973; Steiner, 1976). This is not simply the center of the disk since, as a rule, the disks are not symmetrically subdivided. Many features of pattern regulation in imaginal disks after experimental interference become explicable under this assumption. This can be addressed here only briefly; for a more extensive discussion see Meinhardt (1980). Distal transformations are expected whenever cells of all compartmental specifications are brought into contact. This is the case if two fragments, derived from the opposite sides of a wing disk, are fused, but does not happen when such fragments are kept separate (Haynie and Bryant, 1976). Similarly, fragments of the leg disks regenerate removed distal elements only when cells of the dorsal, ventral and of the posterior compartments are all present, as indicated by the results of Schübiger and Schübiger (1978) and Strub (1977a).

The distal regeneration of a fragment completely confined to the anterior leg compartment seems to be a counter-example. However, as we know from the results of Schübiger and Schübiger (1978), such regeneration is connected with a transgression of the A-P compartment border, and structures with posterior specifications are formed. This compartmental respecification leads to a new intersection of compartments and therefore to distal transformation.

The regeneration of cockroach legs (Bohn, 1965; French, 1976) is assumed to be controlled by the same mechanism. Assuming a similar geometry of the compartments as in Drosophila, they have the shape of stripes, oriented along the length of the leg. Removal of a part of a leg leads during closure of the wound to a new intersection and hence to a new morphogen source. All cells exposed to a morphogen concentration higher than that corresponding to their own specification will be reprogrammed according to the new level in the gradient.

Several experimental observations support the concept of a diffusible morphogen and its stepwise, irreversible interpretation. Mutations are to be expected in which the morphogen production is altered but not the response of the cells to it. Such mutations are expected not to be cell-autonomous since a small patch of mutated cells would not alter the positional information, and would participate in the formation of a normal pattern. Two mutations are known which are of this type: the mutation wingless (Morata and Lawrence, 1977) and mad (Jürgens and Gateff, 1979). In the latter, duplicated legs are formed after a heat shock. The subdivision into anterior and posterior leg compartments seems to be normal, but the heat shock causes a second dorsal compartment at the ventral site of a disk, leading to a dorsal-ventral-dorsal subdivision of the anterior compartment. This would lead to two points where all compartments are close to each other and therefore to two proximo-distal axes. An interesting feature is that the duplicated leg can be incomplete. This rules out any model according to which the proximo-distal axis of the leg is formed by an initial determination of the most proximal and the most distal structures with following intercalation of the missing structures. Distally incomplete structures are expected in a gradient scheme whenever the maximum concentration is not reached. One reason could be that the cooperation of the compartments is restricted, since, for instance, too few cells of a particular compartmental specification are available or they are not close enough to one another to allow a sufficient cooperation. This would be the case in the mutant described above if the second dorsal compartment appears as an island in the normal ventral compartment.

The model links the early compartmentalization with the rules of pattern regulation discovered by French et al. (1976). It provides a molecular mechanism for the complete circle rule. Instead of 12, only three or four positional values are assumed to be important for the distal trans-
formation. Three positional values are sufficient to define a handedness and the achievements of the polar coordinate model such as the explanation of supernumerary structures remain valid. The complete circle rule may be substituted by a complete compartment rule. This resolves some experimentally observed violations of the complete circle rule where elements of circumferential positions are missing but distal transformation nevertheless takes place (Schubiger and Schubiger, 1978). The finer subdivisions of the compartments around the circumference as well as along the proximo-distal dimension within a segment are controlled by a different mechanism: Presumably by the direct mutual induction of locally exclusive states (Meinhardt and Gierer, 1980), a mechanism which allows intercalation of missing structures.

Conclusion

The escapement model provides a mechanism for the reliable interpretation of positional information. The embryo becomes subdivided into compartments and in register with this into segments with specific determinations. Activation of particular control genes by counting of structures on the gene level becomes possible. The early compartmental subdivision is exploited differently in thoracic and abdominal segments: In the thoracic segments, the cooperation of compartments leads to the generation of the positional information for the proximo-distal axis of appendages. In the abdominal segments it is assumed that the transient binary subdivision leads to the first elements of an intrasegmental pattern which is completed by the mutual induction of locally exclusive states (Meinhardt and Gierer, 1980). Relatively simple mechanisms can lead to primary pattern formation within an embryo. By its interpretation, a superposition of a sequential and a periodic structure can be formed. This provides the prerequisites for the generation of subpatterns. In this way, the overwhelming structural complexity of a developing organism can be generated in a reproducible way.

References


