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# Positional Information and Pattern Formation [and Discussion]

L. Wolpert and G. Dover

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# Positional information and pattern formation

By L. Wolpert, F.R.S.

*Department of Biology as Applied to Medicine, The Middlesex Hospital Medical School, Cleveland Street, London W1P 6DB, U.K.*

Spatial patterns of cellular differentiation may arise from cells first being assigned a position, as in a coordinate system, and then interpreting the positional value that they have acquired. This interpretation will depend on their genetic constitution and developmental history. Different patterns may thus arise from similar positional fields. The specification of positional value may involve a positional signal, such as the concentration of a diffusible morphogen, but can also depend on how long the cells remain in a particular region, such as a progress zone. Positional values may also be acquired by direct transfer from one cell layer to another, as in directed embryonic induction. Positional value, unlike a positional signal, involves long-term memory, and can be regarded as a type of cell determination. Cells of the same differentiation class may have different positional values and may thus be non-equivalent. Evidence is presented for a signal providing positional information along the antero-posterior axis during chick limb development. This signal has properties similar to those of a diffusible morphogen.

## Introduction

Pattern formation can be viewed as the spatial organization of cellular differentiation (Wolpert 1971). This distinguishes it from the two other main processes in development, cellular differentiation and changes in form. For example, in the development of the vertebrate skeleto-muscular system the same classes of cellular differentiation occur again and again, such as differentiation into muscle and cartilage. The pattern problem is concerned with their spatial localization. Changes in form during development often involve a localized group of cells exerting contractile forces as in neural tube formation or in the sea urchin gastrulation (Gustafson & Wolpert 1967). Pattern formation is concerned with the specification of those cells that will generate these forces. Thus while differences in adhesiveness can guide tissue movements and lead to particular patterns of cell association (Steinberg, this symposium), pattern formation is the process whereby these differences in adhesiveness arise. Pattern formation should be viewed as assigning to cells specific states that determine their differentiation and other properties, such as their adhesiveness.

## Positional information

The mechanism for pattern formation based on positional information assumes that cells are assigned position as in a coordinate system and then interpret this positional information according to their genetic constitution and developmental history (Wolpert 1971). Such a mechanism has several important implications. The mechanism whereby the pattern is made overt is by the process of interpreting the positional information. There is thus no direct correspondence between the observed pattern and the set of positional values that the cells acquire. In fact the same positional field can be used for very different patterns. Since the observed pattern arises by cell differentiation of the cells according to their position, there need

be no interactions in the system other than those required to specify the coordinate system and the cells' position in it. There need be no interaction between the different elements of the pattern as such.

Several different mechanisms have been proposed whereby cells could have their position specified. The simplest mechanism is one based on the concentration of a signal substance. If the concentration of such a substance was fixed at a boundary region and decreased monotonically with distance from this boundary, then in principle the concentration profile could provide the cells with positional information. This could be achieved with a diffusible morphogen whose concentration was fixed at the boundary and which was broken down at a rate proportional to its concentration, giving an exponential profile. It is not, however, necessary to have a localized source, and Meinhardt & Gierer (1974) have shown how a gradient in a morphogen could be set up autonomously with appropriate molecular interactions. A feature of all positional fields is that they are always small, less than about 1 mm when they are set up, and that it takes times of the order of hours to set them up (Wolpert 1971). It was these features that led Crick (1970) to suggest a diffusible morphogen as the basis for setting up positional fields. It is attractive to think of a diffusible signal passing between cells via gap junctions; all developing positional fields have gap junctions, but evidence that they provide the channel for signalling is still absent (Wolpert 1978). It is thus of importance that Babloyantz (1977) has shown that a concentration gradient capable of providing positional information can be generated in a system in which the cells can influence each other by contact interaction: the molecules on the surface of one cell affecting the rates of reactions in its neighbours without any actual transfer of molecules.

It is also possible to specify position by means of a mechanism based on time (Summerbell *et al.* 1973). The essence of this mechanism is that cells measure how long they remain in a growing region of fixed dimensions: a progress zone. Since the size of the region is constant, cells are continually leaving the zone and if the measurement of time is autonomous there will be a correlation between the distance between cells and how long they had remained in the progress zone. Other mechanisms for specifying position could be based on cell counting (Wolpert & Gingell 1969) or the phase difference between two signals (Goodwin & Cohen 1969), but there is little or no experimental evidence to support them.

A somewhat different mechanism for specifying position is based upon direct transfer. The idea is that one tissue that already has a positional field can transfer its set of positional values to a competent tissue. It is suggested that this is the basis of directive embryonic induction.

One particular class of pattern probably not based on positional information is that of spacing. Here a set of similar structures, such as bristles in insects, form a pattern with varying degrees of order, in which the basic feature is that there is a minimum distance between the structures. In the case of bristles and hairs in insects, this probably arises from an inhibitory mechanism: existing structures prevent the formation of similar structures close to them (Lawrence 1970). There may be homology between such an inhibitory signal and a positional signal.

A characteristic feature of many developing systems is their capacity to regulate when parts are removed (Cooke 1975). It is this characteristic that in part has given rise to the concept of an embryonic field. In terms of positional information a field may be defined as that set of cells that have their position specified with respect to the same boundary regions. Regulation can thus be considered in terms of specifying new positional values when part of the system is removed (Wolpert 1971). The classical distinction between morphallaxis and epimorphosis can be understood in these terms. In morphallaxis, new positional values are specified without





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growth. Thus, if the boundary region is removed in hydra, a positional value corresponding to the boundary region will form at the cut surface, and new positional values will be specified with respect to it (Wolpert *et al.* 1974). In principle, most of the existing positional values will be altered and interactions will tend to be long-range (but not greater than about 1 mm). By contrast, in epimorphosis the changes in positional value are generated by growth from a localized region. Most positional values will remain unaltered and interactions will be short-range. A formal model for epimorphosis is provided by the polar coordinate model (French *et al.* 1976).

Since positional fields are usually very much smaller than the structures that they finally give rise to, it must be that a great deal of development after specification of the field is autonomous, or involves a different class of mechanisms or interactions. It also implies that cells remember their positional values.

## Positional value and non-equivalence

Positional value is the long-term memory of position and must be distinguished from any positional signal by which it is specified. Positional value can be regarded as a cell parameter that characterizes a cell in as important a manner as overt cell differentiation (Wolpert 1981). It is in some ways analogous to cell determination. It also has the important property of making cells of the same differentiation class non-equivalent (Lewis & Wolpert 1976). This, in turn, is what distinguishes a pattern-forming mechanism based upon positional information from one based upon a pre-pattern or a temporal sequence.

A mechanism based on a pre-pattern supposes the variation in some morphogen homologous with the observed pattern (figure 1). Then if two regions of the pattern have the same class of cells, such as cartilage, there is no intrinsic difference between the cells of these two regions, they are equivalent. By contrast with a mechanism based upon positional information, cells with different positional values can give rise to the same cell types. There will thus be an intrinsic difference between these cells, making them non-equivalent.

Evidence for non-equivalence comes from a variety of experiments, particularly regeneration studies. The structures regenerated when the limb of a urodele is amputated, depends on the level of the cut. Only the cells close to the cut surface are involved and there are no long-range influences. Since the cell types in the limb do not vary along the limb axis, it may be inferred that there are intrinsic differences along the axis, reflecting different positional values, making the cells non-equivalent and leading to different patterns of regeneration (Bryant 1978). This is particularly clear in intercalary regeneration in the cockroach leg (Bohn 1970), where there appears to be a continuous set of positional values along the axis of the tibia: when grafts are made such that normally non-contiguous positional values are placed adjacent to one another, intercalary regeneration occurs so as to restore a smooth set of positional values. This intercalation is dependent only on the positional values at the cut.

This type of regeneration and intercalation is epimorphic since the new positional values arise by growth from a localized region. It has been formalized by French *et al.* (1976) in the polar coordinate model. Here positional values are encoded in terms of polar coordinates, and rules are given as to how the system behaves. The important point here is that the related experimental evidence provides substantial evidence for positional value as a cell parameter, since epimorphic regeneration, or intercalation, provides a biological assay and shows that cells respond in a particular way, according to their positional value and not their class of cell differentiation.




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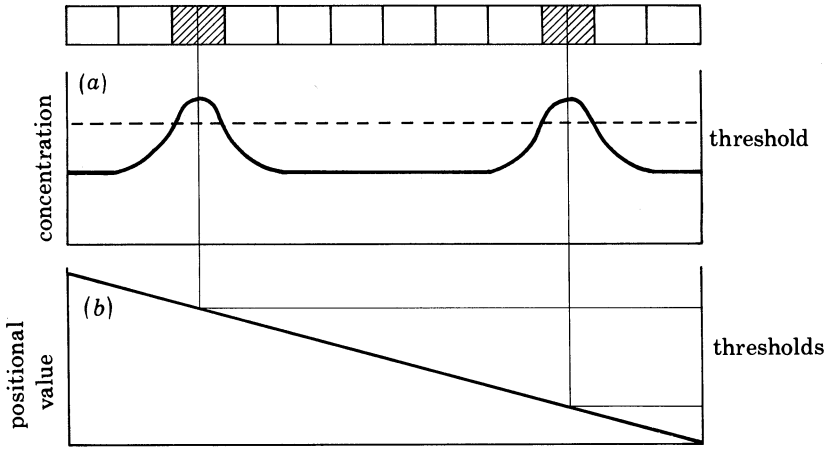


FIGURE 1. The distinction between a mechanism for pattern formation based on a pre-pattern and positional value. For the pre-pattern model (*a*) cells differentiate if the concentration of a morphogen is above a given threshold. The cells that differentiate are equivalent. If the cells differentiate at two different positional values as in (*b*), the cells are non-equivalent.

## THRESHOLDS AND INTERPRETATION

We know neither how positional value is recorded within the cell nor how it is interpreted. Nevertheless, it does not seem unreasonable to assume that an early step in the interpretation process involves a threshold mechanism: above a critical concentration of some substance some internal switch of the cell, such as a gene, is on, whereas below it, it is off. The sigmoidal response of allosteric enzymes does not easily provide a basis for such a mechanism. We have put forward a model based on positive feedback – in some ways analogous to the threshold for conduction of the nerve impulse – which provides a sharp threshold as well as memory (Lewis *et al.* 1977). The model assumes that a gene is activated by a signal substance, such as a morphogen, and the gene product itself activates the gene, thus providing a positive feedback loop. From this rather simple system one obtains kinetics such that at low concentrations of the morphogen the gene is effectively off, but at a critical concentration of the morphogen the gene is turned on permanently, even when the morphogen concentration is reduced to zero. The precision of such a mechanism is dependent on how accurately cells can specify their own thresholds, and this in turn will depend on how accurately they can control the concentration of their own macromolecules. This is not known. Concentrations of small molecules could be averaged out by the presence of gap junctions.

A more complex model for the activation of specific genes at specific concentrations of the morphogen has been put forward by Meinhardt (1978).

## POSITIONAL SIGNALLING IN THE CHICK LIMB

The development of pattern within the chick limb can be viewed in terms of positional information. We have suggested that position is specified in a zone at the tip of the limb bud, the progress zone, and that different mechanisms are used for the proximo-distal and antero-posterior axes (figure 2). For the proximo-distal axis we have proposed a mechanism based on how long the cells remain in the progress zone (Summerbell *et al.* 1973) whereas for the antero-posterior axis we have suggested that there is a positional signal, possibly a diffusible morphogen (Tickle *et al.* 1975). The signal comes from the polarizing region, discovered by Saunders & Gasseling (1968) and located at the posterior margin of the bud. If the polarizing region is the




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source of a morphogen whose concentration is kept constant, and the morphogen is broken down at a rate proportional to its concentration then an exponential diffusion gradient will be set up. This gradient can provide positional information along the antero-posterior axis (figure 3*a*) (for review, see Tickle 1980).

The pattern of digits, normally *2 3* and *4*, provides a very convenient marker along the antero-posterior axis. These digits arise largely from the posterior half of the limb bud. If an additional polarizing region is grafted to the anterior margin, the resulting pattern of digits is *4 3 2 2 3 4*, as would be expected if a mirror-image gradient were set up (figure 3*b*). Several points relating to this basic experiment must be emphasized. (i) The polarizing region itself does not contribute to the new structures, it merely acts as a signalling region (Smith 1979). (ii) While digits are convenient markers, all other structures are affected. Muscle and tendons, for example, are also duplicated (Shellswell & Wolpert 1977). More proximally, one may find

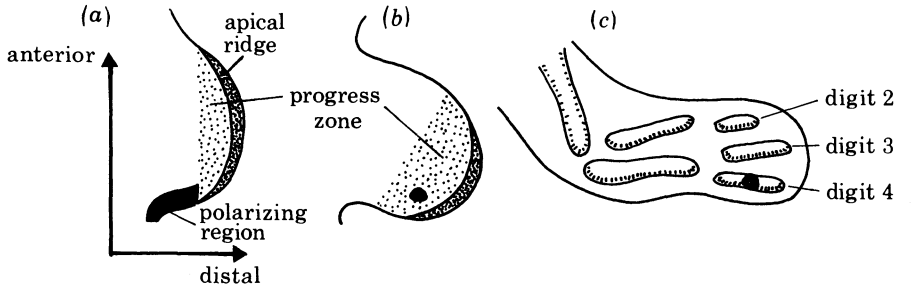


FIGURE 2. Diagram of the early development of the wing bud to show the region involved in the specification of positional information: (*a*), (*b*) and (*c*) show successive stages. In (*c*) the early cartilaginous elements begin to appear. The group of cells in the progress zone in (*b*) acquire positional values such that they form part of digit *4*.

either two ulnas or ulna radius ulna. (iii) The level at which duplication starts depends on the stage at which the polarizing region is grafted (Summerbell 1974). (iv) There is considerable widening of the limb bud after a polarizing region graft. (v) Leg polarizing region or polarizing region from other amniotes provide the same signal (Fallon & Crosby 1977).

We have explored the effect of grafting the polarizing region at different positions along the antero-posterior axis, and in general these correspond quite well with the expected pattern (Summerbell & Tickle 1977). Thus if the polarizing region is grafted near the middle of the limb, the expected pattern of digits is *2 3 4 4 4* (figure 3*c*) and the usual result is *2 3 4 4*. If it is grafted near the host's polarizing region then the pattern is unchanged, presumably because the source keeps the concentration constant.

While the results of such grafts fit the morphogen model quite well, they can also be accounted for by a model based on intercalation of positional values (Wolpert & Hornbruch 1981). The essential difference between the two models is that a positional signal would be expected to alter positional values of adjacent tissues, whereas with intercalation no positional values would be lost. We have exploited this difference by grafting one polarizing region at the anterior margin of the limb bud and then grafting a second further polarizing region at successive positions along the antero-posterior axis. On an intercalation model the same structures should always form between the two grafted regions, whereas with a signal the pattern will depend on the distance between them. We have found the latter to be true. Thus as the distance between the grafted polarizing regions decreases, digit *2* no longer forms between them.

As pointed out above, after a polarizing region graft, the limb bud widens. This widening




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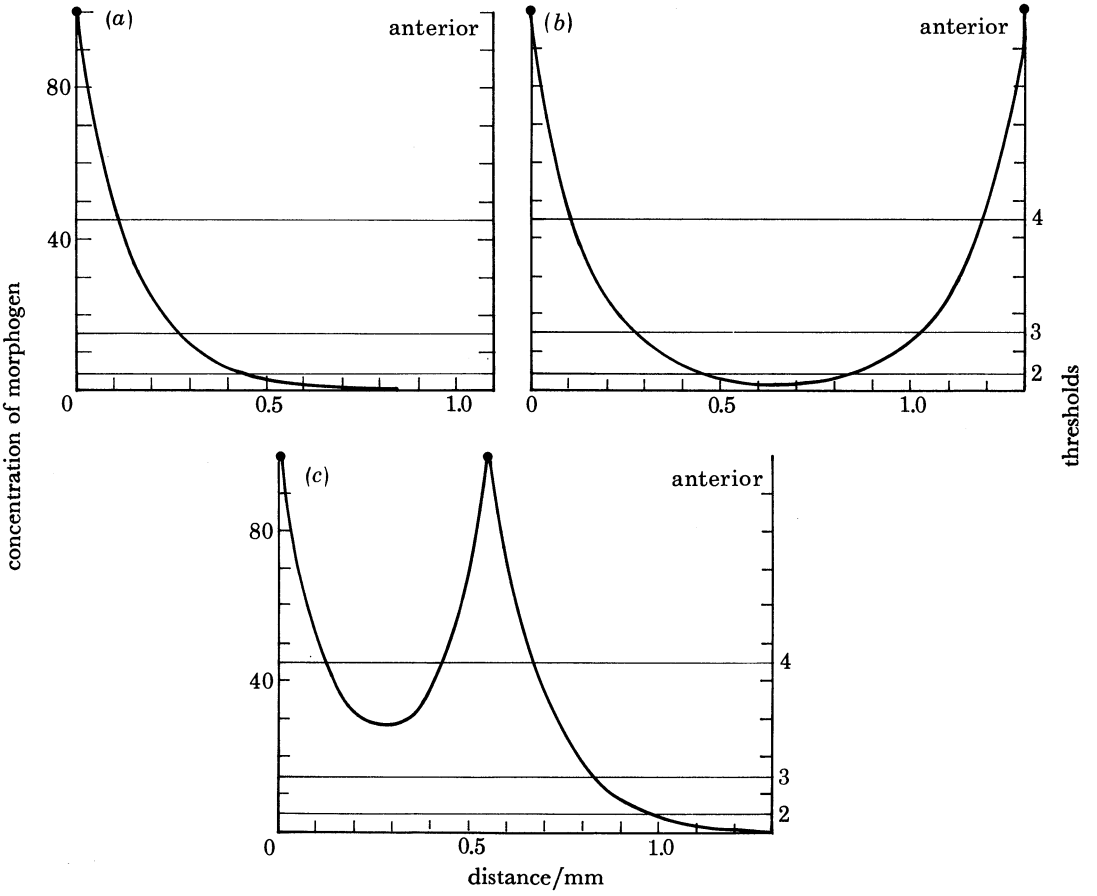


FIGURE 3. Diagrams to illustrate the specification of the digits by a diffusible morphogen from the polarizing region (indicated by ●). (*a*) The pattern in the normal limb. (*b*) The pattern when an additional polarizing region is grafted to the anterior margin. (*c*) The polarizing region is grafted near the centre of the limb. It is assumed that the distance between the polarizing regions increases by 50 % after grafting.

starts about 8 h after the graft has been made and by 36 h the limb bud is 50 % wider (Smith & Wolpert 1981). Remarkably, there is no effect on the proximo-distal growth. This widening has important implications for a signalling mechanism as it alters the distance between the host and grafted polarizing regions. In fact, if widening did not occur we would expect the two polarizing regions to be too close together to allow digit *2* to form. That this is indeed the case is shown by irradiating limb buds so as to prevent widening, and the pattern of digits is now typically *4 3 3 4* (Smith & Wolpert 1981).

These experiments support the view that the signal can alter local positional values and exerts its influence over a distance of several hundred micrometres. Direct evidence for this comes from Honig (1981), who interposed leg tissue between the grafted polarizing region and the wing tissue, and found that the influence of the polarizing region could be propagated over several hundred micrometres. Summerbell (1979) has interposed impermeable barriers between the host polarizing region and the rest of the wing and found that digits were lost in a manner consistent with a diffusible signal.

A crucial test for a signalling model is whether or not the signal can be attenuated. If it is attenuated, we should expect that when grafted to the anterior margin, instead of obtaining *4 3 2 2 3 4*, *3 2 2 3 4* or *2 2 3 4* should result. This is just what is found when the polarizing is

exposed to increasing doses (up to 80000 rad) of γ-rays (Smith *et al.* 1978). This attenuation has been shown more directly by Tickle (1981) in two ways. First, she showed that by diluting polarizing region cells with non-polarizing region cells, attenuation occurred. She then showed that polarizing region cells spread as a monolayer on a tiny piece of plastic were capable of signalling and that the number of cells correlated with the structures formed. About 150 cells were needed for digit *4*, about 70 for digit *3* and only about 30 for digit *2*. These numbers correspond well with the results from the dilution experiments if it is assumed that only cells immediately adjacent to the apical ridge can signal.

Taken together, these results strongly support the idea of a propagated signal from the polarizing region specifying position along the antero-posterior axis. However, it must be emphasized that they do not provide direct evidence for a diffusible morphogen being the signal. In fact, the prediction of broad structures in the central region of a mirror image duplicate, where the gradient would be very flat, has not been observed.

There are important similarities between the polarizing region and the early development of the primary pattern in certain insects such as *Euscelis*. Sander (1981) has shown that by moving posterior cytoplasm from the posterior pole to different positions along the egg axis results in patterns directly comparable with those found in the chick limb. These have been modelled by Meinhardt (1977), who has shown that the gradient in inhibitor generated by a reaction–diffusion mechanism can account for most of the results. There are also important similarities to the action of the micromeres in early development in the sea urchin.

## Induction and the transfer of positional information

The essential feature of induction is that one tissue in an embryo can influence the fate of another tissue with which it comes into contact. The classic examples are the induction of the nervous system by the underlying mesoderm, and the induction of the lens by the eye cup. There are many examples of the mesoderm inducing the overlying ectoderm (see review by Kratochwil 1972). If the 5 day chick corneal epithelium is combined with dermis from a feather-forming region, then feathers develop from the epithelium. Again, if the mesemchyme of the dental papilla of the mouse is combined with epithelium from the foot of a 14 day mouse embryo, the epithelium forms an enamel organ. These are examples of what Saxen (1977) has called directive embryonic induction.

I suggest that directive embryonic induction can be best understood in terms of the transfer of positional information. In essence, the idea is that positional information is initially specified in a two-dimensional cell sheet, the mesoderm in vertebrates, and that when this mesoderm comes to underlie the ectoderm, positional information in the ectoderm is specified by direct transfer of positional values from mesodern to ectoderm (figure 4). This makes the positional fields in two tissues congruent. It is of great interest that the Willshaw & von der Malsburg (1979) model for the establishment of retino-tectal connections is based, in part, on the retinal cells inducing their own postional value in the tectal cells with which they come into contact. The mechanism involves, essentially, the transfer of diffusible marker molecules from the retina to the tectum.

If the ectoderm acquires its positional field from the underlying mesoderm, the structures formed will reflect the interpretation of these positional values. In these terms, the positional field would be the same in different species and only the interpretation would change. This is




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just what is found by transplantation between species (see review by Holtfreter & Hamburger 1955). The larval newt has a pair of balancers on the ventro-lateral part of the head, whereas the toad tadpole has no balancers but a pair of suckers in a ventral position. The larval newt has teeth, whereas the tadpole has horny denticles. Reciprocal transplants of embryonic ectoderm between these orders have shown that structures appropriate to the grafted ectoderm form in the correct position. Thus when belly ectoderm from the toad is grafted to the head region of the newt embryo, suckers and a horny mouth develop. The ectoderm acquires its positional value and interprets it in the appropriate manner.

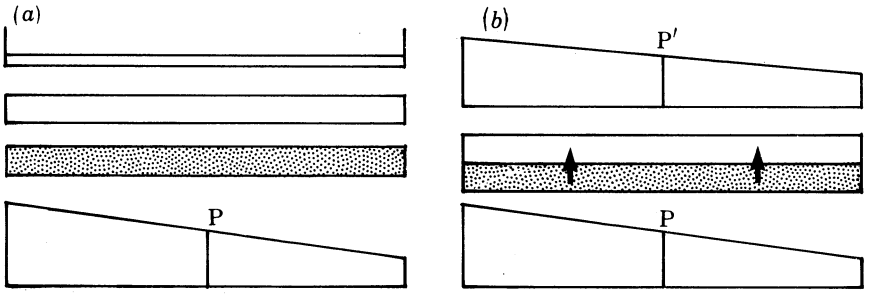


FIGURE 4. Diagram to illustrate the transfer of positional information in directive embryonic induction. In (*a*) only the lower sheet of cells has a graded set of positional values. When the tissues are brought into contact (*b*) the induced tissue acquires a similar set of positional values to that of the inducing tissue.

Another striking example of cells acquiring their positional values from the same field comes from pattern coloration in birds. Melanoblast differentiation is position-dependent. Rawles (1948) has shown that irrespective of the immediate source of the melanoblasts, if they are introduced into foreign feather germs, both the pattern and colour are consistently that of the donor species: introduction of Plymouth Barred Rock melanophores into White Leghorn gives the Plymouth Barred Rock pattern. The simplest explanation is that the melanophores acquire the positional value of the ectoderm and interpret this in an appropriate manner.

The similarity between these phenomena and genetic mosaics of pattern mutants such as *aristapaedia* should be emphasized and point again to common positional fields (Postlethwait & Schneiderman 1974).

## CONCLUSIONS

The concept of positional information can provide a useful framework for considering a variety of pattern-forming systems. The essence of the idea is that positional value partly defines the state of a cell. Unfortunately we have no idea whatsoever as to the molecular basis of positional value or of the positional signals that may be involved. Attempts to approach this problem by trying to block the signal from the polarizing region with specific inhibitors of biochemical processes have not been very successful (Honig *et al.* 1981). They merely served to show, for example, that the signal was completely blocked by inhibitors of RNA synthesis at concentrations at which no reduction in bulk RNA synthesis could be detected. At this stage we lack a suitable assay to do the appropriate biochemistry.

At the level of phenomenology, the models are quite successful. There is also good evidence that positional fields in different insect imaginal discs are the same (Postlethwait & Schneiderman 1974; Bryant 1979). The idea of common positional fields occurs repeatedly and there is good evidence, as discussed above, from studies on pigment patterns in birdsand early amphibian




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development. By treating directive induction as the transfer of positional value, a wide range of additional phenomena can be accounted for. However, it must be recognized that this is largely a redescription of the phenomena in new terms. But it means that if, and when, positional value is understood in molecular terms we shall have the key to a large class of different patterning processes.

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## *Discussion*

G. Dover (*Department of Genetics, University of Cambridge, U.K.*). There seems to be a loose interchangeability in Professor Wolpert's use of positional information and positional value. I understand that information is a parameter derived from a signal such as a diffusing morphogen, whereas value is a property of a cell in response to the information. Different cells acquire different values as a consequence of their, say, genetically determined response to the strength or duration of the signal. This being so, I am a little surprised that Professor Wolpert's interpretation of the results of embryonic induction experiments is described in terms of a transfer of positional value from one cell layer to another. This might be so if the value determinants were epigenetic and mobile, but in the absence of any information on this it is easier (and more in keeping with his concept of universal signals) to say that the host cells are responding (i.e. developing their own species-specific values) to a common signal present in the donor. This then would be described as information rather than value transfer.




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