Switch genes and sex determination in the nematode

_C. elegans_

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**SUMMARY**

The development of the nematode _C. elegans_ is highly invariant, and has been described in great detail. Many developmental mutations have been isolated and analysed; some of these identify switch genes, i.e. genes that control the choice between two developmental alternatives. It appears that the genetic controls of development in this animal are discrete, hierarchical and relatively simple. The control of sexual dimorphism provides an example of how a series of switch genes are organized in a regulatory cascade.

**INTRODUCTION**

_Caenorhabditis elegans_ is a small free-living nematode, about 1 mm long as an adult, which occurs naturally as part of the interstitial fauna in soil from many different parts of the world. In the laboratory, it is easily cultured on agar plates, using _E. coli_ as a food source; under these conditions it grows rapidly, with a 3½-day generation time at room temperature. It is an extremely simple animal: although it has a well-defined and invariant anatomy, including differentiated muscles, nerves, intestinal cells and so on, the total number of somatic nuclei in the adult hermaphrodite is only 959, and in the adult male (the alternative sexual form) only 1031. These nuclei are generated as a result of an almost wholly
invariant series of cell divisions, so both the process of development and the final adult form are essentially identical from animal to animal. Furthermore, because the animal is small and transparent and grows rapidly, it is possible to visualize all the nuclei in the living animal at any time by means of Nomarski interference microscopy, and consequently to follow all processes of cell division, migration, and differentiation as they occur in real time, by direct observation. These advantages have been exploited by Sulston and coworkers to yield the complete cell lineage of this animal. An initial phase of embryonic divisions in the egg yields at hatching a larval hermaphrodite containing precisely 556 somatic nuclei and 2 germ cell nuclei (Sulston, Schierenberg, White & Thomson, 1983). Post-embryonic growth through the four larval stages is accompanied by further somatic cell divisions, mainly involved with sexual maturation of gonadal and nongonadal structures (Kimble & Hirsh, 1979; Sulston & Horvitz, 1977). The germ cell nuclei also proliferate within the gonads to yield approximately 300 sperm and 1000 oocytes in the hermaphrodite, or 2500 sperm in the male.

The animal is also very simple in genomic terms. The haploid DNA content is 80,000 kb, about half the size of the *Drosophila* genome (Sulston & Brenner, 1974). Estimates of gene number are also low: a total of possibly less than 3000 loci are required for viability (Brenner, 1974). The technical advantages of hermaphroditic reproduction and short life cycle have led to the rapid accumulation of genetic data, so that more than 450 genes have been mapped so far, and increasingly powerful genetic methods have been developed (Riddle & Swanson, 1982). Much of this work has been aimed at understanding the genetic basis of development. *C. elegans* is a particularly favourable subject for developmental genetics because the descriptions of wild-type anatomy and development permit detailed comparison of normal and mutant phenotypes. Furthermore, the process of development in mutant animals can be examined directly, so that deviations from the wild-type pattern can be seen as they occur, rather than by being deduced from retrospective analysis of an altered final structure in the adult.

In trying to understand the overall logic of the genetic programme underlying development, it is important to concentrate on genes that play key roles in the process. A simple failure to execute part of development correctly can occur as the result of many different kinds of mutation, most of which will have little to do with the controlling factors that govern wild-type morphogenesis and differentiation. For example, defects in pyrimidine biosynthesis caused by rudimentary mutations of *Drosophila* (Norby, 1970) result in an abnormal wing shape, but it is unlikely that the rudimentary locus has any morphogenetic functions in the wild-type fly. More probably the altered wing shape is a secondary consequence of a simple growth defect caused by pyrimidine starvation during the development of the wing. Analysing mutations of this kind will do little to increase our understanding of development.

A better strategy is to study mutations that transform development, causing
Table 1. Developmental switch gene characteristics

<table>
<thead>
<tr>
<th>Genotype of switch gene</th>
<th>Fate of cell one</th>
<th>Fate of cell two</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Dominant gain-of-function mutation (e.g. overproducer or constitutive)</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Recessive loss-of-function mutation (e.g. hypomorph or null: amber, deficiency etc.)</td>
<td>B</td>
<td>B</td>
</tr>
</tbody>
</table>

Switch genes of this type have been recognized for some time among the homoeotic genes of *Drosophila*. For example, there are the opposite transformations of wing and haltere caused by the dominant *Cbx* mutations and the recessive *bx* mutations of the *bithorax* complex (Lewis, 1978). The paradigm set out in Table 1 has also been demonstrated for several genes in *C. elegans*. Three examples will be outlined, illustrating the control of developmental choice in space, time, and sex. The control of sexual dimorphism will then be reviewed in more detail.

**SWITCH GENES IN C. ELEGANS**

1. A homoeotic gene: *lin-12*

The gene *lin-12* is implicated in controlling spatial diversification in many different tissues of *C. elegans*, as shown by Greenwald, Sternberg & Horvitz (1983). The genetic properties of this locus, and the cell lineages and cell fates affected by it, are described in detail by these authors. The behaviour of three postembryonic blast cells in the male provides an illustration of the effects of *lin-12* mutations (Fig. 1). These three cells, called P9.p, P10.p, and P11.p, lie in the posterior ventral hypodemis and undergo different division patterns in the wild.
type, resulting in different adult structures. Dominant mutations of \textit{lin-12}, which appear to result in overproduction of \textit{lin-12} gene product, cause all three cells to adopt the '2°' division pattern, while null mutations cause both P9.p and P10.p to adopt the '3°' division pattern. The adult structures generated by these cells are correspondingly altered: a characteristic ectodermal structure called the hook is formed by P10.p descendants in the wild type, and it was found that \textit{lin-12} null mutants form no hook, while \textit{lin-12} dominant mutants form three hooks.

Several other loci that may correspond to nematode homoeotic genes, affecting a variety of different cell lineages, have been identified (Horvitz \textit{et al.} 1983). Most of these genes have discrete effects, affecting only one group of cells or, in the case of more pleiotropic loci such as \textit{lin-12}, affecting different cells in analogous ways. This suggests that much of the underlying programme is organized on a modular basis.

Fig. 1. A homoeotic gene. The effect of mutations in \textit{lin-12} on the cell lineages produced by three blast cells in the male ventral hypodermis. The vertical axis represents time (not to scale). After Greenwald \textit{et al.} (1983).
2. A heterochronic gene: lin-14

A class of control gene has been identified by Ambros & Horvitz (1984) that appears to govern the relative timing of many events during postembryonic growth. These have been termed 'heterochronic' genes. The most thoroughly analysed of these is lin-14. As with lin-12, many (but not all) of the blast cells are affected in analogous ways. Dominant lin-14 mutations cause retardation of development, so that parts of the lineage appropriate to earlier larval stages are repeated inappropriately at later stages. Recessive lin-14 mutations cause precocious development, so that particular division patterns appear inappropriately early. The effects of mutations in lin-14 are illustrated in Fig. 2 using the blast cell T of the hermaphrodite, which normally gives rise to a set of identified neurons and hypodermal cells. Additional or defective sets of descendant cells are generated by the mutants, as shown. Ambros & Horvitz (1984) have also shown that the hypodermal cells of these mutants produce temporally inappropriate differentiated structures, by examining the cuticle morphology in electron microscope sections. In the wild type, different larval stages produce ultrastructurally distinct cuticle. Dominant lin-14 mutants have retarded cuticle characteristics, while recessive lin-14 mutants have precocious cuticle characteristics.

3. A sex-determining gene: tra-1

C. elegans occurs naturally in two sexes, the self-fertilizing hermaphrodite and

Wild type  \[\text{lin-14 (dominant):} \] gain of function, (retarded)  \[\text{lin-14 (recessive):} \] loss of function, (precocious)

Fig. 2. A heterochronic gene. The effect of mutations in lin-14 on cell lineage for the hermaphrodite blast cell T. After Ambros & Horvitz (1984).
the male. Females are not found in the wild, but do occur in closely related species such as *C. remanei* (Sudhaus, 1974). Comparison of *C. elegans* hermaphrodites with *C. remanei* females suggests that hermaphrodites differ from females only in the germline: hermaphrodites produce a few hundred sperm at

![Diagram of hermaphrodite and male](image)

**Fig. 3.** Schematic diagrams of hermaphrodite and male.

<table>
<thead>
<tr>
<th></th>
<th>Hermaphrodite</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomes</td>
<td>5AA;XX = 12</td>
<td>5AA;XO = 11</td>
</tr>
<tr>
<td>Germline</td>
<td>ca. 300 sperm, 1000 oocytes</td>
<td>ca. 2500 sperm</td>
</tr>
<tr>
<td>Gonad structure (total nuclei)</td>
<td>Two arms (143)</td>
<td>One arm (55)</td>
</tr>
<tr>
<td>Body (total nongonadal nuclei)</td>
<td>816</td>
<td>976</td>
</tr>
<tr>
<td>Sex-specific features:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodermis</td>
<td>Vulva</td>
<td>Copulatory bursa, spicules, rays, etc.</td>
</tr>
<tr>
<td>Muscles</td>
<td>16 nuclei (uterine &amp; vulval)</td>
<td>41 nuclei (copulatory)</td>
</tr>
<tr>
<td>Neurons</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>Sense organs</td>
<td>–</td>
<td>Bursal rays, papillae, cephalic sensilla, etc.</td>
</tr>
<tr>
<td>Intestine</td>
<td>Yolk protein synthesis</td>
<td>–</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Egg-laying</td>
<td>Mating</td>
</tr>
</tbody>
</table>
the beginning of gametogenesis before changing over to oogenesis. However, there are many differences between hermaphrodites and males, summarized in Table 2 and Fig. 3. Embryonic development is almost identical in the two sexes, differing only in two sets of programmed cell death that occur late in embryogenesis. Much more extensive differences emerge subsequently, which involve most of the postembryonic divisions and result in adult forms exhibiting many differences in gonadal and nongonadal anatomy (Sulston & Horvitz, 1977; Kimble & Hirsh, 1979; Sulston, Albertson & Thomson, 1980). Also, an anatomically monomorphic structure, the intestine, synthesizes large quantities of yolk protein in the adult hermaphrodite but not in the male (Kimble & Sharrock, 1983).

Primary sex determination in the wild type is chromosomal: the hermaphrodite has two X chromosomes (XX) while the male has one (XO). However, mutations in a single autosomal gene, \textit{tra-1}, will override the chromosomal mechanism, as summarized in Table 3. Dominant \textit{tra-1} mutations, which appear to result in constitutive activity, cause both XX and XO animals to develop into females, and null mutations cause both XX and XO animals to develop into males (Hodgkin, 1983b). Females are animals identical to hermaphrodites except that they fail to make sperm; the germ cells normally destined for spermogenesis undergo oogenesis instead.

Many different dimorphic characters have been examined in the \textit{tra-1(dom)} XO mutant females and the \textit{tra-1(null)} XX mutant males, and all show sexual transformation (Hodgkin & Brenner, 1977; Hodgkin, 1980, 1983b). Characters that are identical in the two sexes are unaffected. Thus, all aspects of sexual differentiation are under the control of this single gene activity.

**CONTROL OF \textit{TRA-1} ACTIVITY**

The fact that constitutive \textit{tra-1} mutations (of which there are now more than ten) cause both XX and XO animals to develop into females as opposed to hermaphrodites, implies that this gene must be regulated in both XX and XO wild-type animals. In XO animals, the action of this gene must be entirely repressed in order to permit male development, and in XX animals it must be partly repressed in order to permit spermogenesis to occur in an otherwise female body. How is this regulation achieved? So far, six genes have been identified that mediate between the primary sex determination signal, X

<table>
<thead>
<tr>
<th>Genotype</th>
<th>XX phenotype</th>
<th>XO phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>hermaphrodite</td>
<td>male</td>
</tr>
<tr>
<td>\textit{tra-1(dom)}</td>
<td>female</td>
<td>female</td>
</tr>
</tbody>
</table>
chromosome dosage, and the gene tra-1. Most of these genes were initially identified fortuitously (Klass, Wolf & Hirsh, 1976; Hodgkin & Brenner, 1977; Nelson, Lew & Ward, 1978), but subsequently efficient screens or selections for sex determination mutations have been developed (e.g. Hodgkin, 1980; Doniach & Hodgkin, 1984), so that many mutations (between four and sixty) are known for each gene. Therefore, this class of gene may be approaching saturation.

All of these genes have effects on sexual phenotype in both soma and germ-line. The effects of recessive loss-of-function mutations in the seven genes are summarized in Table 4. In most cases amber alleles or genetic deficiencies or both have been identified, so that for five of the genes (tra-1, her-1, tra-2, tra-3, and fem-1) it is fairly certain that these are the null phenotypes. The two remaining genes, fem-2 and fem-3, are as yet less thoroughly analysed. The seven genes are distributed apparently at random over four of the five autosomal linkage groups of C. elegans (indicated by Roman numerals in Table 4), showing no evidence of functional linkage.

Epistatic interactions between the different genes have been worked out by constructing double mutants and examining the resultant phenotypes. These single and double mutant phenotypes provide evidence for a regulatory pathway shown in Fig. 4, consisting of four steps. At the first step, the X-chromosome dosage (or more precisely the X chromosome to autosome ratio, as shown by Madl & Herman (1979)) controls the activity of the gene her-1. At the second step, her-1 activity controls the activity of the two genes tra-2 and tra-3 (acting

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Somatic phenotype</th>
<th>Germline phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XX</td>
<td>XO</td>
</tr>
<tr>
<td>Wild type</td>
<td>hermaph.</td>
<td>male</td>
</tr>
<tr>
<td>her-1 V</td>
<td>hermaph.</td>
<td>hermaph.</td>
</tr>
<tr>
<td>tra-2 II</td>
<td>abn. male</td>
<td>male</td>
</tr>
<tr>
<td>tra-3 IV</td>
<td>hermaph.</td>
<td>hermaph.</td>
</tr>
<tr>
<td>fem-1 IV</td>
<td>fem-2 III</td>
<td>fem-3 IV</td>
</tr>
<tr>
<td>tra-1 III</td>
<td>male</td>
<td>male</td>
</tr>
</tbody>
</table>

| X/A     | her-1 | tra-2 | tra-3 | fem-1 | fem-2 | fem-3 | tra-1 |
| ratio   |      |      |      |      |      |      |      |
| Low (XO male) | ON  | OFF  | ON   | OFF  | ON   | ON   |
| High (XX hermaphrodite)| OFF | ON   | OFF  | ON   | ON   | ON   |

Fig. 4. Basic model for gene interactions controlling tra-1 activity, and proposed states of gene activity in wild-type sex determination. See text for explanation.
Nematode switch genes and sex determination

At the third step, the activity of \textit{tra-2} and \textit{tra-3} controls the activity of the three \textit{fem} genes. At the fourth step, \textit{fem} gene activity controls \textit{tra-1} gene activity. Interactions at each step are negative: a high X/A ratio represses the \textit{her-1} gene, \textit{her-1} gene activity represses \textit{tra-2} and \textit{tra-3}, and so on. Consequently, this set of genes can exist in two states, corresponding to the two wild-type sexes, as shown in Fig. 4. The gene activities are represented as ‘ON’, or ‘OFF’ symbolizing the presence or absence of active gene product, but it is possible that the states are really ‘high’ and ‘low’ rather than ‘on’ and ‘off’. Also, the molecular nature of these regulatory interactions is unknown. The activity of a gene can be regulated at many different levels, from pre-transcriptional DNA rearrangement to post-translational modification of the gene product, and formal genetic analysis can provide little information about which of these levels is involved.

The basic model adequately explains the somatic phenotype of the various mutants, and also of double mutants (see Hodgkin, 1980; Doniach & Hodgkin, 1984). A further series of multiple mutant constructions is summarized in Table 5: this confirms that mutations at different steps interact in a strictly hierarchical manner, at least for the somatic phenotype. Mutations at any step epistatically suppress mutations at previous steps. Independent evidence for a sequence of steps acting in the proposed order comes from experiments on temperature-sensitive (ts) mutations. Ts mutations are known for genes at the first (\textit{her-1}, Hodgkin, 1980), second (\textit{tra-2}, Klass \textit{et al.} 1976), and third (\textit{fem-1}, Nelson \textit{et al.} 1978) steps, and temperature-shift experiments have been carried out for all of these. The \textit{ts fem-1} allele affects only gonadal development, so comparison between the three genes is limited to the somatic gonadal phenotype. Temperature-sensitive periods for the three genes occur in the predicted order, as shown in Fig. 5.

The control of germline phenotype is more complicated. First of all, the double mutant \textit{fem-1(-);tra-1(-)} is somatically male, but fails to make any sperm and instead differentiates oocytes in an otherwise male gonad (Doniach &

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Genotype & Somatic phenotype & & Germline phenotype & \\
& XX & XO & XX & XO \\
\hline
Wild type & hermaph. & male & hermaph. & male \\
Single mutant: \textit{her-1} & hermaph. & hermaph. & hermaph. & hermaph. \\
Double mutant: \textit{her-1; tra-2} & abn. male & male & male & male \\
Triple mutant: \textit{her-1; tra-2; fem-1} & hermaph. & hermaph. & female & female \\
Quadruple mutant: \textit{her-1; tra-2; fem-1; tra-1} & male & male & female & female \\
\hline
\end{tabular}
\caption{Hierarchical relationships among sex-determining mutations}
\end{table}
Hodgkin, 1984). Similar behaviour is seen with *fem-2* and *fem-3* mutations. This means that the *fem* genes have a dual role: they must act both to repress *tra-1* activity and to promote spermatogenesis. Secondly, *tra-1* activity appears to repress spermatogenesis, because constitutive *tra-1* mutants fail to make sperm irrespective of the state of the *fem* genes. Thirdly, there must be an additional control specifically affecting the XX germline that permits spermatogenesis to occur in the wild type hermaphrodite, because otherwise *tra-1* would always be fully active in an XX animal, so spermatogenesis could not occur. Several lines of evidence suggest that this control involves transient modulation of *tra-2* activity. Most strikingly, dominant *tra-2* mutations have been isolated that appear to affect only the XX germline: hermaphrodite spermatogenesis is eliminated, so that XX animals develop into fertile females and XO animals develop into fertile males (T. Doniach, unpublished observations).

Fig. 5. Temperature sensitive periods for gonad development. The upper curves show a temperature-shift experiment for the *ts* mutation *her-1(e1561)*. Eggs or larval worms of a strain, genotype *her-1(e1561) dpy-21(e428)*, were shifted from 15° to 25° (shift-up, circles) or from 25° to 15° (shift-down, squares), at defined times relative to hatching (time 0). Adult XO worms were recognized by the absence of a dumpy phenotype, because *dpy-21* is not expressed in XO animals (Hodgkin, 1983c), and these animals were scored for normal (male) gonadal and nongonadal development. An average of 30 animals were examined for each time point. The data plotted here show the percentages of XO animals with male somatic gonad anatomy. The bars in the lower part of the figure show the temperature sensitive periods inferred for *her-1(e1561)*, for *tra-2(b202)* (Klass *et al.* 1976), and for *fem-1(hc17)* (Nelson *et al.* 1978).
These considerations lead to a more complex model, shown in Fig. 6. This model also includes a weak direct interaction (see below) between the X/A ratio and tra-I, indicated by the dotted line. It is possible that some of the complexity is a consequence of the way this species has evolved. Probably the ancestor of *C. elegans* was a nematode with a male/female sex determination system, which is the usual arrangement in this phylum. Evolution from a female sex to a hermaphrodite sex requires that control of germline sex be uncoupled from control of somatic sex, and therefore additional regulatory interactions would need to evolve.

The model as it stands provides only a formal description of the interactions between the genes, and leaves many questions unanswered. For instance, what is the molecular nature of these interactions? How is the initial signal, the X-chromosome-to-autosome ratio, measured? How is tra-2 modulated in order to achieve spermatogenesis in hermaphrodites? How are the two different states of the pathway maintained? These questions will probably remain unanswered until the sex determination genes can be analysed in molecular terms.

**MINOR INTERACTIONS; CANALIZATION**

A conspicuous feature of the phenotypes of developmental mutants in any organism is their variability. This is particularly noticeable in *C. elegans*, because the wild-type phenotype is so highly invariant. By contrast, mutants show a more variable phenotype (Horvitz & Sulston, 1980). For example, *tra-I(−) XX* animals are invariably male in nongonadal anatomy, but the gonadal anatomy is abnormal in about one third of the individuals, and the fertility of the anatomically normal *tra-I XX* males is lower and more variable than that of wild-type XO males. Similarly, the fertility of *her-I(−) XO* hermaphrodites is very variable. Minor canalizing interactions can be invoked to explain this variability. These interactions may normally act to strengthen the genetic switch mechanism, making it resistant to environmental perturbation. When mutation forces the organism to cope with an unphysiological situation, such as the absence of *tra-I* gene product in an XX animal, the consequences may be more variable as a result of the action of minor but conflicting influences.
Some of these minor interactions in the sex determination pathway can be identified: for example, there is evidence for a weak direct effect of the X/A ratio on \textit{tra-1} activity (Hodgkin, 1980). Also, there is evidence for interaction between sex determination and dosage compensation, which may affect the fertility of XX males or XO hermaphrodites (Hodgkin, 1983c). It should be stressed that the major interactions are adequate to explain most or all of the phenomena observed in the wild type, and that the minor interactions only become conspicuous in certain mutant combinations. 'Fine tuning' of this kind can be expected to turn up when any genetic regulatory mechanism is examined in detail.

**DOWNSTREAM FUNCTIONS**

How does \textit{tra-1} activity control the many different processes involved in sexual maturation? It is conceivable that the product of this gene is a hormone, or controls the synthesis of a hormone, but this hypothesis is unlikely, for several reasons. Laser ablation experiments have shown that the sexual phenotype of many different parts of the body is maintained in an autonomous manner (Sulston & White, 1980 and personal communication; Kimble & Sharrock, 1983). Also, there exist sex determination mutants with tissue-specific abnormalities such as the \textit{tra-1} allele \textit{el488}: XX animals homozygous for this allele have hermaphrodite gonads and intestinal cells in an otherwise male body. These results would not be expected if sexual phenotype were controlled by a diffusible substance such as a hormone. It is more likely that sexual phenotype is determined in a cell-autonomous manner, as in \textit{Drosophila} (Baker & Belote, 1983).

The \textit{tra-1} gene product probably acts within cells to control, directly or indirectly, the expression of a variety of target genes. Some of these can already be identified, such as the switch gene described earlier, \textit{lin-12}. Some dominant \textit{lin-12} mutations cause the male ventral hypodermal cells (P3-6.p) of XO animals to divide in a manner appropriate to the hermaphrodite, forming 'pseudovulvae' (Greenwald \textit{et al.} 1983). Also, mutations in a heterochronic gene, \textit{lin-28}, similar to \textit{lin-14}, cause certain cells in the XX animal to divide in male-specific lineage patterns (Ambros & Horvitz, 1984). It follows that both of these genes are probably under the direct or indirect control of \textit{tra-1}. Another putative switch gene which acts at many different times and places during development is \textit{ced-3}: loss-of-function mutations in this gene result in the survival of most of the cells that would normally undergo programmed cell death (Horvitz, Ellis & Sternberg, 1982). It is likely that this gene is involved in the choice between programmed cell death and survival, and it too may be under \textit{tra-1} control, because the sex-specific embryonic cell deaths fail to occur in \textit{ced-3} animals.

These three genes are required for many different events during the development of both sexes. There exist also less pleiotropic genes which appear to be necessary only for certain developmental events in one sex or the other. A search
for male-specific mutants revealed the existence of a series of mab (male abnormal) mutations (Hodgkin, 1983a), some of which appear to affect only male development. For example, the mab-9 mutation affects the division patterns of the nongonadal blast cells B, U, and F, which divide only in the male, and does not affect any of the hermaphrodite lineages. The converse class, mutations that affect the hermaphrodite but not the male, is represented by some of the egl (egg laying defective) mutations (Trent, Tsung & Horvitz, 1983).

Finally, there are genes involved in gametogenesis. Some of these make abundant products, such as the yolk proteins, and are therefore very amenable to molecular analysis. A gene family coding for the major yolk proteins has been cloned and partially sequenced (Blumenthal et al. 1984). The yolk proteins provide a good example of a differentiated end product, being synthesized only in a specific tissue (the intestine), at a specific stage (the adult) and only in one sex (the hermaphrodite). In time, it may be possible to work out all of the separate spatial, temporal and sexual controls that underlie an event such as the synthesis of yolk protein.

CONCLUSION

The genetic analysis of development in simple invertebrates such as C. elegans and Drosophila has led to the identification of major developmental control genes in both these organisms. The view that development occurs as a result of the harmonious integration of a very large number of gene activities, none of which alone has a particularly significant effect, is not tenable for these animals. Instead, we can identify single genes that play essential roles in determining which developmental paths are pursued by a cell or group of cells, and we can begin to trace the regulatory interactions that control these major genes. These interactions may be complicated, as in the sex determination pathway described above, but the complexity is not beyond analysis by present methods.

On the other hand, some of the phenomena exhibited by developing systems seem to be most easily explained by global properties, rather than by the action of particular genes at specific times or places. For example, there are the morphogenetic events of early embryogenesis, and the establishment of positional information within developmental fields, perhaps by means of morphogen gradients. However, particular gene activities must be required for the synthesis of morphogens and determining the shape of the gradient; similarly in setting up the cytoskeletal machinery within the egg that then executes gastrulation and so forth. In these areas it may actually turn out that most of the properties are generated by the interaction of a small number of gene products, and that genetic analysis of these phenomena will prove illuminating.

Switch genes comparable to those of C. elegans and Drosophila have not been identified in vertebrates, but this failure may merely reflect the lack of detailed genetic analysis and the difficulty of interpreting mutant phenotypes in these
more complicated and regulative animals. With more sophisticated genetic methods, and with better descriptions of the cellular details of vertebrate development, it is possible that general principles of developmental gene action will become discernible, that apply to mammals as well as to nematodes and fruitflies.

I am grateful to Tabitha Doniach, Iva Greenwald, and John Sulston for discussion and comments on the manuscript, and to Robert Horvitz and his colleagues for communication of unpublished results.

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