Drosophila development

Compartment genes in hand

from Peter A. Lawrence

THE history of *Drosophila* genetics is long and full of happenstance. Typically, mutations were chanced on in one decade, mapped immediately, written down, written up and written off — unless they became useful in mapping other things in later decades. Analysis of the normal function of the gene that carries the mutation was usually not attempted or even thought of, and only recently has it become common practice to use systematic mutagenesis to find out whether the original mutation is typical of mutations in the gene or a freak. A good example is provided by the history of the *engrailed* gene; papers appearing in this issue of *Nature*[1] and in the current issue of *Cell*[2,3] take the gene into the era of molecular cloning.

The *engrailed*[1] (*en*[1]) mutation was reported in 1929 (see figure) but it took more than 40 years for the gene to be recognized as rather special. That story began when Ed Lewis pointed out to Antonio Garcia-Bellido that the posterior edge of the wing of flies carrying the *en*[1] mutation is transformed into an anterior margin. Following Tokunaga's study of the leg[4], Garcia-Bellido and Santamaria[5], using mosaic flies, showed that *en*[1] cells affect posterior but not anterior margins of the wing. A year later Garcia-Bellido, Ripoll and Morata discovered that the wing is made in two precise compartments, each being constructed of all the descendants of a small founding group of cells[6]. They suggested the groups are distinct because they express, and are subject to, a set of regulatory genes, called 'selector genes'[7]. This key idea provided a link between genetics and pattern formation, and prompted a search for such genes, of which *engrailed* was suggested to be one.

Morata and I tested this idea and showed that *en*[1] has no detectable effect on any cell in the anterior wing compartment, but seems to alter every cell in the posterior compartment. We also suggested that the *engrailed* gene 'labels' posterior cells so that they do not mingle freely with anterior cells[8,9] — the idea being that the compartment border at the interface between anterior and posterior cells is straight because (like oil and water) the different cell populations keep their contact to a minimum[10]. The *engrailed* gene is therefore presumed to be responsible for the compartment border itself. We also suggested that when the gene is first activated in development, the patches of active cells need not be arranged very precisely, because uneven lines would automatically straighten as development proceeds[11]. The *engrailed* gene therefore became a keystone in the compartment hypothesis and has remained an ever-present and enigmatic lodger in our lives.

About ten years ago, Thomas Kornberg began to study the gene. He made the first lethal allele of *engrailed* (*en*^{C2}) in Cambridge and then made a thorough genetic analysis of the locus, collecting a large number of mutants and studying their embryonic phenotype[12]. It was shown that cells homozygous for a mutation that is lethal to the fly are nonetheless perfectly normal when experimentally placed in any anterior compartment (not just the wing) of a heterozygote fly but abnormal in posterior compartments[12,13]. These and several other studies[14,16] supported our view that *engrailed* is a selector gene largely or entirely responsible for the differences between anterior and posterior compartments.

The molecular biology of the *engrailed* gene has been pursed for several years by Kornberg, O'Farrell and their colleagues. But it is the recent discovery of the homoeo box by the groups of Walter Gehring in Basel and Matthew Scott in Boulder that has opened up an effective route to the cloning of selector genes. Fjose, McGinnis and Gehring have now followed this route to the *engrailed* gene[1]. And Kornberg's group has obtained the same gene by more traditional means[2,3]. Even more pleasing is what both groups have been able to show by virtue of having isolated the gene.

First, using the *in situ* methods developed for *Drosophila* by Akam[17] and by Hafen *et al.*[18] they have shown that *engrailed* is active in the embryo from early gastrulation onwards and is expressed in the form of circumferential stripes. Both groups have assumed, but not demonstrated, that the active bands coincide with the posterior compartments (Kornberg and colleagues show that the gene is transcribed in posterior compartments later on — for example in the wing disk). Both groups show pictures of the stripes in the main body of the embryo. The total number of stripes is not clear (nor, because frozen sections spoil the anatomy of the older embryos, is the precise identity of the transcribing cells known) but, nevertheless, both groups count 14 stripes in the main body of the embryo, which is exactly the number of metameric units counted by Poulson many years ago[19]. (I write metameric units because probably these cell masses are not segments as Poulson thought, but "parasegments" — units consisting of a posterior compartment of one segment plus an anterior compartment of the next[20].)

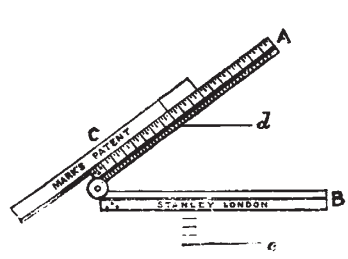
Both groups show that the stripes in which *engrailed* is outlined are about half as wide as those in which it is not, which suggests that the posterior compartments are smaller than the anterior ones. This is shown directly for the first time. (Indirect estimates based on clone frequency and gynandromorphs had shown that there are more anterior precursor cells than posterior ones[2].) Activity of the *engrailed* gene can first be detected at gastrulation, at which time Kornberg *et al.* show that the posterior stripe is only 1–2 cells wide. If we are correct that *engrailed* product is crucial

100 years ago

A LINE-DIVIDER

GALILEO'S proportional compasses are said to date from the year 1597. We infer that the instrument consisted of two arms, jointed as in the accompanying figure, so that one arm could move freely about the joint, Each arm had a number of equal divisions (not necessarily of the same length on each arm), the zero point being at the joint. To divide a given length into five equal parts is it necessary to take an ordinary pair of compasses and measure the given length with these, then set the proportional compasses so that the fifth division on each arm may be at the given distance apart, then transfer with the ordinary compasses the distance between the unit divisions—this will be one-fifth of the given line. This seems to have been the manner of using the instrument employed by Galileo (cf. Marie, *Histoire des Sciences Mathématiques et Physiques,* tome iii. p. 108). Other modes of using will doubtless occur to most of our readers. The principal involved in this and similar instruments, and certainly in the one before us, is that of the proportionality of corresponding sides in similar triangles.

Our figures represents Miss Marks's patent line-divider for dividing and spaces into a number of equal parts. A B forms a hinged rule with a firm joint; each limb is ten inches in length (in the specimen we are describing), the limb B is bevelled, fronted with brass, and presents a straight edge, so that straight lines can be drawn along it. The limb A is also bevelled, and is divided on the bevelled edge and also on the top



into eighty equal parts, so that we are enabled to divide a given length into any number of equal parts from two to eighty. A is fitted to slide in an undercut groove upon the plain rule C, which has a single line marked upon it, and is also provided with needle points on the underside, to prevent if from slipping when placed in any position.

From *Nature* 31 275, 22 January 1885.