The 1995 Nobel Prize in Medicine: A tribute to the power of formal genetics

One of the most remarkable areas of achievements in biology during the past few decades has been the elucidation of the mechanisms that an apparently unstructured egg cell uses to transform itself into a complex patterned multicellular organism. The first glimpse of this genetic blueprint was obtained through genetic studies with the fruit fly Drosophila. Fortunately, these results were obtained at a time when the revolution in DNA and molecular biological techniques were spreading like wild fire and therefore, even these esoteric genetic studies with Drosophila attracted the attention of biologists working with all kinds of organisms. Very soon the commonality of organization of all living organisms was confirmed and scientists could hope to decipher the genetic programme that controls development of an complex organism as Homo sapiens.

Therefore, the committee for this year's coveted Nobel prize in Medicine has very rightly selected three Drosophila geneticists for their pioneering work on the genetic control of embryonic development and differentiation using simple but powerful tools of conventional genetic analysis. They are Edward B. Lewis of The California Institute of Technology, USA, Christiane Nüsslein-Volhard of the Max-Planck Institute for Entwicklungsbiologie, Tübingen, Germany and Eric Wieschaus of Princeton, USA. Lewis has been working with Drosophila, mostly by himself, for more than 50 years and published a summary and analysis of the data collected by him over many years in his well-known Nature paper in 1978; Nüsslein-Volhard and Wieschaus published their seminal paper, also in Nature, in 1980 when both were at the EMBO Laboratory in Heidelberg, Germany. These two papers have changed the course of contemporary biology in more than one way by allowing a new look at the transformation of a seemingly unstructured egg into a complex, patterned and organized organism. The concepts generated in these papers have found very wide applications in studies dealing not only with animals but plants as well. It is remarkable indeed, that these two papers were based on simple methodologies of 'pure' or formal genetics with no 'sophisticated' or 'advanced' molecular biological techniques being employed. As is the wont of geneticists, they simply obtained a large number of mutations, selected those that affected early development, mapped the mutations on linkage maps and characterized the consequences of either individual mutations or specific combinations of the different mutations on the developmental phenotype of the individual. The only 'advanced' analytical techniques employed by these scientists were scanning electron and/or dark field microscopy. It was the systematic analysis and a foresight in rationalization of the phenotypic effects of the various mutant genes that led them to formulate general principles of Nobel prize-winning consequence.

Study of embryonic development has fascinated biologists for a long time. Curiosity to know how a single cell develops into a complex organism led to the growth of the whole field of Embryology to describe the morphological and anatomical changes taking place in a developing embryo. In biology it is often necessary to examine the abnormal so that the normal may be understood. Thus a conventional experimental embryological approach to the study of a complex process has been to disrupt one step in the chain of events and follow its consequence. This path was followed by generations of classic embryologists during the century and their efforts did help in providing some

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cause-effects relationships in the complex events taking place during embryonic development. However, none of these approaches could address the central question of which molecules actually cause a particular cell in the embryo to decide or to know that it belongs to any head or tail region of the future animal or the leaf or root of the plant. With the growing realization that like all other things in living organisms, the development was the under genetic control, a geneticist would approach this issue by inducing random mutations in genes and identifying, not only the gene that has mutated but also the consequence of that mutation on the phenotype of the individual. It is this approach that led the three Nobel-prize winning scientists to provide the first insights into the complex signaling and regulatory events that 'tell' the undifferentiated cells to be committed to and follow a particular path of differentiation during early embryonic development.

To appreciate and understand the significance of these two papers, we need to briefly look at the way the Drosophila embryo develops (it is interesting to note that the basics of Drosophila embryology were properly understood only because of these and other subsequent papers, yet to understand these papers today we first need to look at what was historically learnt later: this highlights the fraught intuition of these scientists as well as the power of genetic analysis). Unlike any other well-studied case of embryonic development, the Drosophila embryo follows a very unusual pattern of cleavage divisions during which only the nuclear divides repeatedly without any cell division; this results in a syncytial blastoderm stage which quickly cellularizes. This is followed by the demarcation, along the antero-posterior axis, of the repeating units of a defined number of body segments (patterning) with the visible segment boundary bisecting each segment. As a result, each anatomical segment includes the posterior half and the anterior half of consecutive parasegments. Depending upon the antero-posterior and dorso-ventral coordinates, cells in each half (compartments) of the segment are committed to generate specific adult structures. A variety of genetic studies had established that even at the syncytial blastoderm stage, much before the morp-
logical segments become apparent, each modern "strain" of its location in the embryo and also what its "face" is going to be when the cells begin differentiation. The time gap between this "commitment" and "differentiation" can in fact be several days long. The basic question of how the nuclei in the syngastic blastoderm of Drosophila know their location and their fate was addressed through genetic studies. Although Lewis worked much earlier than Nüsslein-Volhard and Wieschaus, the genes that Lewis studied are called upon their duties later in embryonic development than the sets of genes described by the other two. Nüsslein-Volhard and Wieschaus argued that genes that control early embryonic development (and thus affect the critical determination events) if mutated, should cause modified embryos and therefore be embryonic lethal. Therefore, they generated, through conventional mutagenesis procedures, a large number of random mutations in Drosophila genotypes and selected those that led to defects in embryos. A simple microscopic examination of these dead embryos helped them determine the defects in the normal developmental pattern and thereby decipher the role of the mutated gene in the process (see Figure 1). In summary, Nüsslein-Volhard and Wieschaus showed that these sets of genes are sequentially activated after fertilization: i) the "gap" genes define by their expression, the three major domains (antero-median, middle and posterior) along the length of the embryo so that a mutation in any of these genes results in the loss of a contiguous series of structures along the antero-posterior axis; ii) the "pair-rule" genes, working after the "gap" genes, commit the nuclei in one of the 14 separating segments along the length of the syngastic blastoderm; these were called "pair-rule" genes since they seemed to work in alternate segments and a mutation in any of these genes caused alternate, odd or even-numbered, segments to be defective, and iii) the "segment-polarity" genes which finally commit a blastoderm nuclei to the anterior or to the posterior compartment of a given body segment so that a mutation in any of these genes disrupts the polarity in each segment. These three sets of genes thus shown to "context" the blastoderm nuclei their polar co-ordinates and thereby dictate

Figure 2. A typical four-winged fly generated in Lewis experiments when certain bithorax mutant alleles were brought together in heterozygous combinations: such a combination of the mutant alleles lead to a hemisected transformation of the meta-thorax into meta-thorax so that the normally reduced second pair of wings (the halteres) in the meta-thoracic segment now develop into full wings like those in the meso-thoracic segment.

Very early in the growth of Drosophila genetics, a number of homozygous mutations (e.g. the bithorax, antiplodia, proboscipedia) were identified. The existence of homotic mutations suggested that certain genes "tell" the cells at some stage of development as to what they are destined to become and if, in a result of mutation, these genes gave a wrong instruction to a cell, the cell developed a different structure at a wrong place (the homotic transformation). Thus such mutations provide an unique opportunity to ask what these genes "tell" the cell and at what time. Lewis approached this goal by analysing the large number of mutations that mapped to this locus and which transformed a thoracic or an abdominal segment of the fly into another in a complex but predictable fashion. He had earlier shown that this locus is in a complex locus being composed of several discrete genetic units (beause these individual units were initially termed "pseudoloci") which were very closely linked but each had a distinctive effect on the phenotype of thoracic and the abdominal segments. He summarized an enormous wealth of his own experimental data in the 1978

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review published in Nature to show that the different genetic elements comprising the BXC-C control most of the body p. as of the fly. He showed that a chromosome that had lost almost whole of the BXC-C resulted in dysgenesis with all its body segments being similar (no abnormally segmented are formed) and that all optic of the different parts of the BXC-C can be restored in each segment in a defined order. Lewis argued that his results demand that the BXC-C contains a minimum of eight genes that "code for substances controlling levels of toxic and abdominal development - a most remarkable point stated by Lewis was that the order of these genes in the BXC-C was collinear with the structures along the antero-posterior axis of the fly controlled by them. Lewis also argued that each subsequent posterior segment of the body recruits the services of an additional genetic element in the BXC-C linear array. Subse- quent studies (see ref. 4) at molecular and genetic levels, however, revealed that Lewis misinterpreted the dissecting regulatory elements in the BXC-C for structural protein-coding genes: the BXC- C activity has only three structural genes but five regulatory elements that are recruited in a serial fashion to activate one or more of the structural genes of the BXC-C, each of which can produce more than one kind of message due to alternative processes- sions of the primary transcripts. However, this misinterpretation does not in any way undermine the far-reaching impli- cations of his conclusions that the BXC-C genes specified the developmental pathways to build the characteristic pattern of the different body parts and that these genes worked locally. The BXC-C and other homoeotic genes (like the Antennapedia-complex or ANTP- C) are also called as the selector genes which take over from the segmental polarity genes and select the specific structures that each compartment has to elaborate as the embryo continues its development.

While working with BXC-C, Lewis dis- covered another set of genes that con- trolled the development of the melanotic parts of the fly. These genes were also homoeotic in nature and were involved in the development of the homeotic genes. The BXC-C and other homoeotic genes work together to control the development of the different body parts. The BXC-C contains a minimum of eight genes that "code for substances controlling levels of toxic and abdominal development - a most remarkable point stated by Lewis was that the order of these genes in the BXC-C was collinear with the structures along the antero-posterior axis of the fly controlled by them. Lewis also argued that each subsequent posterior segment of the body recruits the services of an additional genetic element in the BXC-C linear array. Subsequent studies (see ref. 4) at molecular and genetic levels, however, revealed that Lewis misinterpreted the dissecting regulatory elements in the BXC-C for structural protein-coding genes: the BXC-C activity has only three structural genes but five regulatory elements that are recruited in a serial fashion to activate one or more of the structural genes of the BXC-C, each of which can produce more than one kind of message due to alternative processesessions of the primary transcripts. However, this misinterpretation does not in any way undermine the far-reaching implications of his conclusions that the BXC-C genes specified the developmental pathways to build the characteristic pattern of the different body parts and that these genes worked locally. The BXC-C and other homoeotic genes (like the Antennapedia-complex or ANTP-C) are also called as the selector genes which take over from the segmental polarity genes and select the specific structures that each compartment has to elaborate as the embryo continues its development.

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Ever since Thomas Hunt Morgan introduced the fruit fly or Drosophila to genetics early in this century, this small insect has been central to the growth of the subject of genetics and thereby to many fundamental concepts in biology. It is interesting to note that Morgan himself was an entomologist who turned to genetics with a view to understanding the central issues of development and differentiation. Although by 1913 Morgan gave up efforts to deal simultaneously with genetics as transmission and genetics as development, it is interesting to note that Morgan's objective of understanding development in terms of genetics has finally been achieved and the power of this approach has been duly recognized by this year's Nobel prize in Medicine.

3. Bauman, W., Materials of the Study of Vascular Plants with a Special Re-


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