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REPRINTS AND REFLECTIONS

The Epigenotype

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The adult characteristics of animals, i.e. their phenotypes, must be studied in order to reach conclusions about the genotypes, i.e. the hereditary constitutions which form the basic subject-matter of genetics. But between genotype and phenotype lies a whole complex of development processes, for which Dr Waddington proposes the name 'epigenotype.' He here describes some of the general characteristics of an epigenotype, with special reference to the fruit-fly *Drosophila melanogaster*.

Of all the branches of biology it is genetics, the science of heredity, which has been most successful in finding a way of analysing an animal into representative units, so that its nature can be indicated by a formula, as we represent a chemical compound by its appropriate symbols. Genetics has been able to do this because it studies animals in their simplest form, namely as fertilized eggs, in which all the complexity of the fully developed animal is implicit but not yet present. But knowledge about the nature of the fertilized egg is not derived directly from an examination of eggs; it is deduced from a consideration of the numbers and kinds of adults into which they develop. Thus genetics has to observe the *phenotypes*, the adult characteristics of animals, in order to reach conclusions about the *genotypes*, the hereditary constitutions which are its basic subject-matter.

For the purpose of a study of inheritance, the relation between phenotypes and genotypes can be left comparatively uninvestigated; we need merely to assume that changes in the genotype produce correlated changes in the adult phenotype, but the mechanism of this correlation need not concern us. Yet this question is, from a wider biological point of view, of crucial importance, since it is the kernel of the whole problem of development. Many geneticists have recognized this and attempted to discover the processes involved in the mechanism by which the genes of the genotype bring about phenotypic effects. The first step in such an enterprise is – or rather should be, since it is often omitted by those with an undue respect for the powers of reason – to describe what can be seen of the developmental processes. For enquiries of this kind, the word 'phenogenetics' was coined by Haecker[1]. The second and more important part of the task is to discover the causal mechanisms at work, and to relate them as far as possible to what experimental embryology has already revealed of the mechanics of development. We might use the name 'epigenetics' for such studies, thus emphasizing their relation to the concepts, so strongly favourable to the classical theory of epigenesis, which have been reached by the experimental embryologists. We certainly need to remember that between genotype and phenotype, and connecting them to each other, there lies a whole complex of developmental processes. It is convenient to have a name for this complex: 'epigenotype' seems suitable[2].

We know comparatively little about the general characteristics of an epigenotype. One general feature, however, is that it consists of concatenations of processes linked together in a network, so that a disturbance at an early stage may gradually cause more and more far reaching abnormalities in many different organs and tissues. Some very beautiful examples of such effects have recently been described by Grüneberg[3,4] based on mutations in his mouse colony at University College, London. One gene, the 'grey-lethal', brings about a lack of yellow pigment in the fur, and a failure of the absorption of bone which normally accompanies growth. The latter effect entails a whole host of secondary consequences. Thus the minerals of the body are immobilized in the bones and cannot be used for new growth, so that the teeth are incompletely calcified and unable to masticate solid food. Again, the lack of bone absorption leads to pressure on some nerves, particularly those serving the lower jaw; this presumably gives rise to neuralgic pain, the animals are disinclined to take even liquid nourishment, the starvation affects the thymus gland, and the animals eventually die. Another lethal gene, this time in the rat, brings about even more manifold and at first sight unconnected abnormalities. The first noticeable effect is an abnormality in the development of cartilage, which affects the ribs, and thus the lungs, circulatory organs, and finally the growth rates of various parts.

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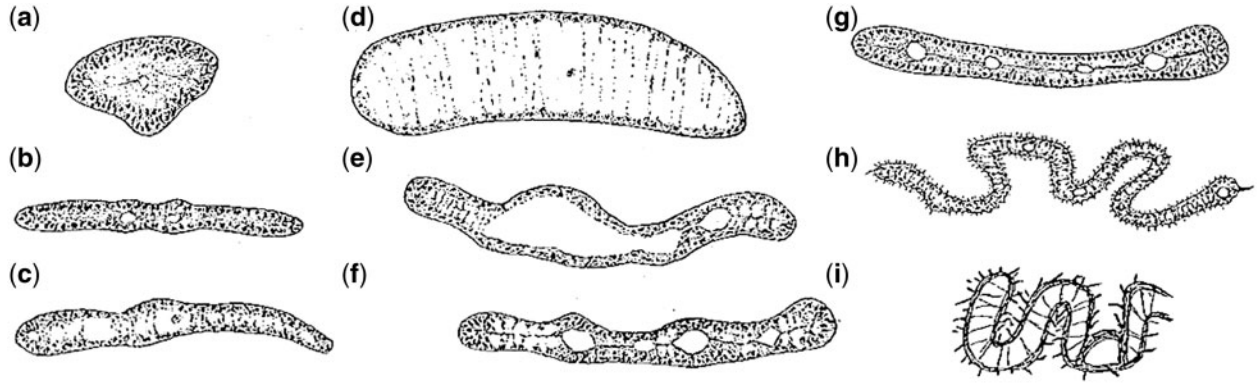


Figure 1 Diagrammatic drawings of sections of the developing wing in the fruit-fly *Drosophila*. Notice how the wing is at first quite solidly constructed. *(*Figure *1b* is of about the same age as figure *2A*.) Then it becomes hollow (figure *1d*, which corresponds to figure *2B*), contracts again (figures 1e, f, g), and finally becomes folded (figures *1h, i*).

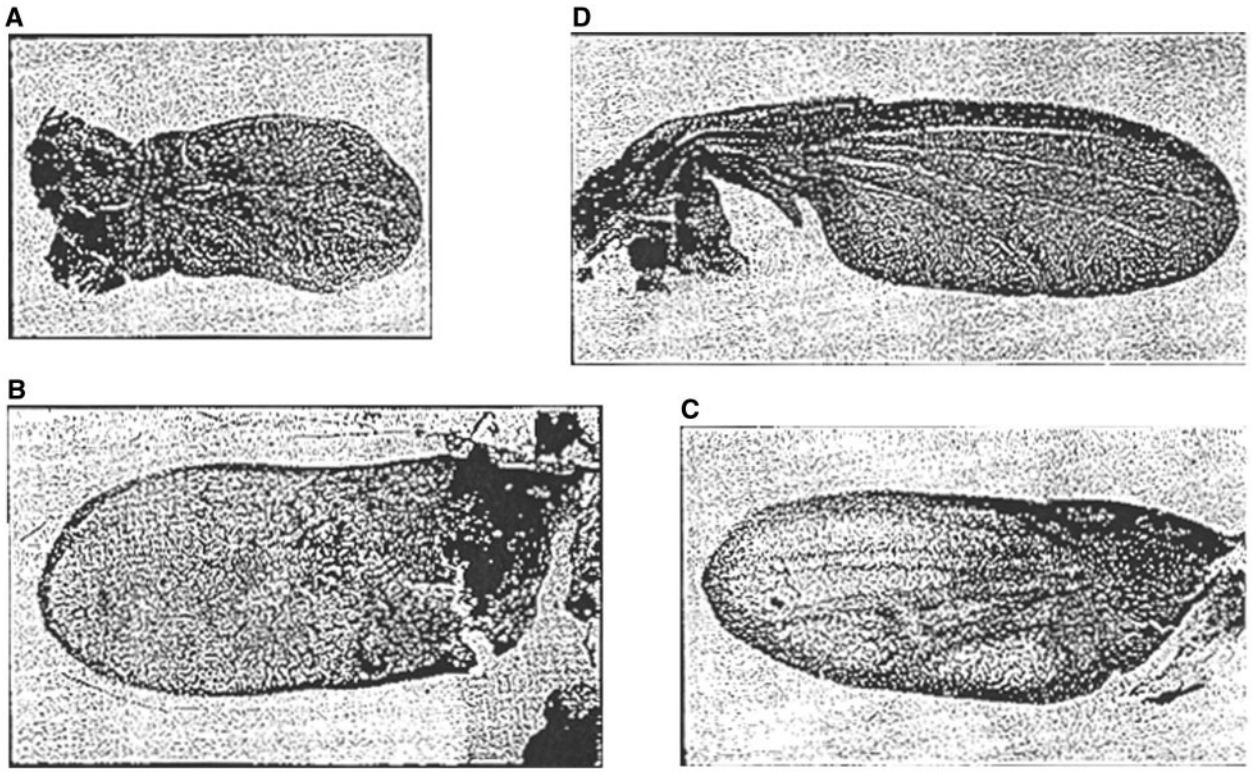


Figure 2 Four stages in the development of the wing in *Drosophila*. Figure *A* shows the wing shortly after the puparium is formed; in *B* the wing has become inflated, and its venation is obliterated; in *C* and *D* it contracts again and its final venation appears. Just after the stage shown in *D*, the wing becomes folded and remains thus until just after the fly emerges from the pupa.

Complementary to the study of single genes and the numerous effects which they produce is the study of a single organ and the numerous genes which affect it. Probably the most completely investigated instance is the wing of that favourite genetical object, the fruit-fly *Drosophila melanogaster*. Following preliminary work by Auerbach, Dobzhansky, and Goldschmidt, I described the developmental actions of some thirty geneloci[5]. It was found that during the first forty-eight hours after the larva enters the pupa, its wings undergo at least fifteen different processes, each of which is affected by some known gene. We

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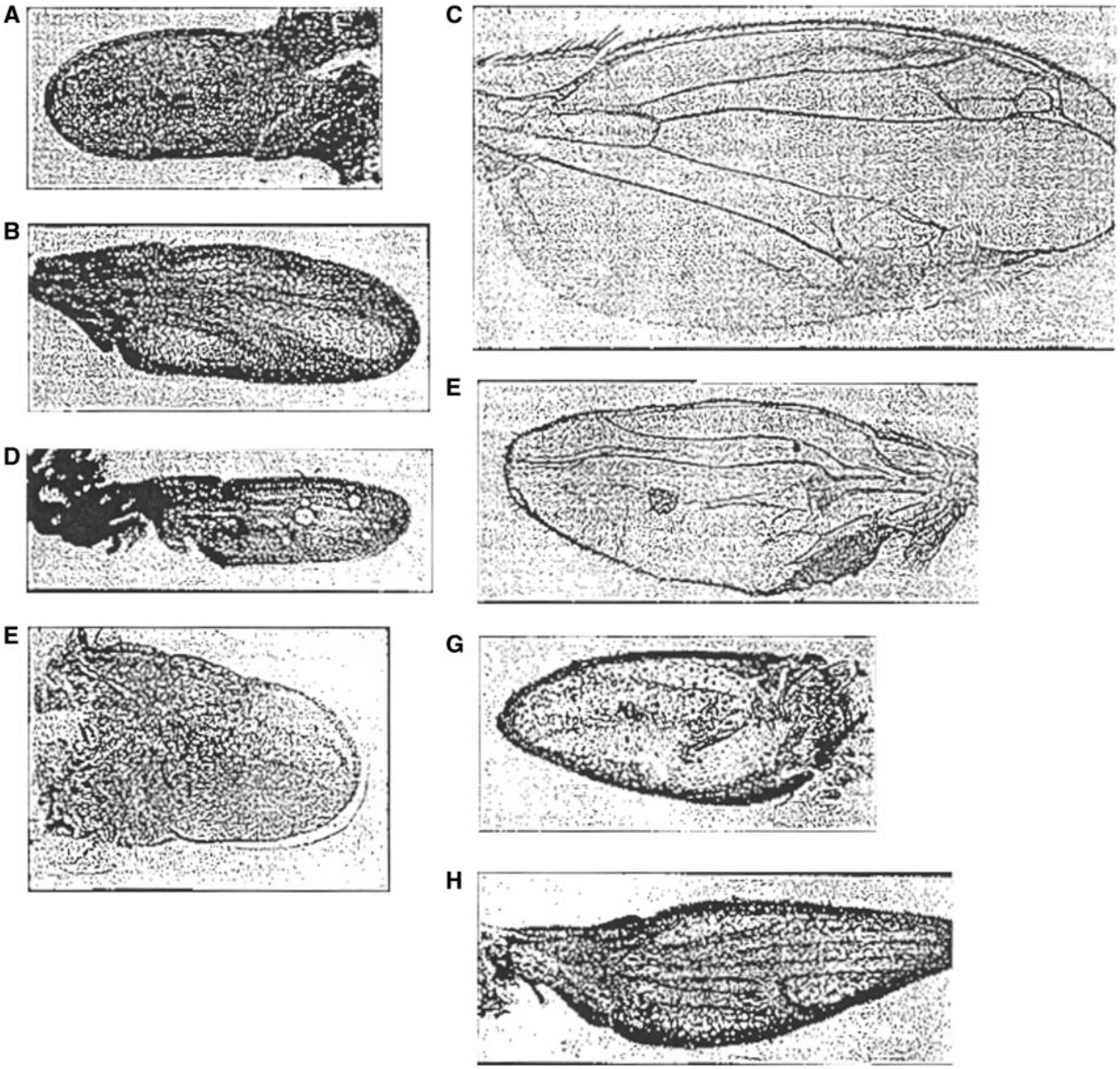


Figure 3 Some genetically controlled abnormalities in the contraction-phase of wing-development in *Drosophila*. Figures *A*, *B*, and *C* show wings of the mutant race *net* in which there is a partial failure of contraction, which causes the formation of extra veins in some regions. In figures *D* and *E* the failure of contraction is much more complete, and bubbles of fluid are left between the two wing-surfaces, which remain so far apart that in many areas no veins appear *(*the mutant *bloated)*. In figures *F*, *G*, and *H* the contraction does not fail, but is abnormal, so that a wing of characteristically elongated form is produced (the mutant *blade* in *D. pseudo-obscura*).

have here, in fact, a concrete example of something which has always been obvious in theory, namely that the genotype is continual and unremitting control of every phase of development. Genes are not interlopers, which intrude from time to time to upset the orderly course of a process which is essentially independent of them; on the contrary, there are no developmental events which they do not regulate and guide.

The alterations in development produced by genetic changes can be used, as the experimental embryologist uses those which he produces by his operating needle, as a means of analysing the causal mechanisms of development. We find, for instance, that is the two sheets of epithelia which build up a *Drosophila* wing fail to come together as they normally do, the cavity left between them may differentiate into a wing-vein instead of into the normal wing surface. Or, again, we find that if the two epithelia are folded together in an abnormal manner, the position of the wrong veins is determined by the upper-surface, and impressed by that surface on to the lower one. These deductions from the 'natural experiments' performed by genes can be checked by

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experiments of the conventional kind; one can make operations on the developing wings, using fine glass needles and the other micro-surgical instruments of experimental embryology. A considerable series of such operations has been made by Lees[6] who was able to confirm, and in some cases to extend, many of the previous deductions.

For this particular organ there remains very little of that gap between genetics and experimental embryology which has been so frequently lamented as one of the main flaws in the structure of biological theory. As would be expected, many of the general principles of experimental embryology reveal themselves again in the epigenetical analysis. For instance, we are familiar with the fact that there are critical periods in development, such as the time of gastrulation at which the primary organizer is active. Similarly we find that in the developmental of the wing there are certain periods at which many deviations of development, which had previously seemed of only minor importance, suddenly entail radical and far-reaching consequences. To give a concrete example: the wing is essentially a sac the two surfaces of which are, at one period, forced apart by a considerable pressure of the contained body-fluid, which is later withdrawn so that the two epithelia come together again. The process of contraction is a critical one. Slight irregularities in it are responsible for most of the abnormalities in the development of the wing-veins, and minor deviations in the relative positions of the wings and legs may, by impeding the flow of body-fluid, lead to crippling malformations of those organs.

It would take us too far to attempt to discuss in detail the general characteristics of such epigenetic crises as these. We should find ourselves involved with the same highly complex and little-understood series of problems which confront the experimental embryologist; with the problem of structures of various ranges of size, with the differentiation of cells and of tissues, and with the question of whether differentiation is into sharply contrasted alternatives or into a continuously varying range of products. Without attempting to answer any of these questions here, we may be content to point out that the analysis of the effects of genes has now progressed far enough to become merged with experimental embryology. The two methods of analysis who *rapprochement* has for so long been no more than a pious hope can now actually and in practice come together in an attack on the still unresolved problems of the epigenotype.

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Commentary: The epidemiology of epigenetics

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We are in the midst of an epidemic of the words 'epigenetic' and 'epigenetics'. In the database of ISI Web of Knowledge, more than a 1300 articles published in 2010 contain epigenetic(s) in their title, whereas the corresponding number for each year prior to 2000 is less than a hundred. Figure 1 illustrates the long-term trend using an index designed to correct for changes in the size and composition of the database. Roughly speaking, there was little change in relative frequency from the 1950s until 1999, but

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