HOMOEOTIC MUTANTS AND EVOLUTION

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About 1950 geneticist R. B. Goldschmidt and paleontologist O. H. Schindewolf independently came to the conclusion that neo-Darwinism was completely inadequate to account for macroevolution. Goldschmidt judged that natural selection only results in preservation of the **status quo** *and that accumulation of mutations with tiny effects could never explain the origin of really new organs and organismal types. Schindewolf judged that the sudden appearance of higher systematic categories in the fossil record and the discontinuities between present and fossil categories were in serious conflict with neo-Darwinism.*

As evolutionists, they came up with an "emergency solution": they decided that macroevolution could be explained only by postulating "macromutations" with large effects, stirring up the whole system. The best examples Goldschmidt could supply were the homoeotic mutants in **Drosophila** *which replace certain organs by entirely different organs. The present author, however, reviews the wealth of data now assembled about homoeotic mutants, and extensively documents that the evidence is only negative with regard to evolution. He concludes that the mentioned criticisms of neo-Darwinism are still as valid as in 1950 but that the alternative ideas have proved to be even worse.*

Introduction

This paper has the same title as an article by the well-known geneticist, Professor Richard B. Goldschmidt.[1] He wrote several papers on the subject because he considered homoeotic mutants to be of major importance to support his peculiar theory of evolution.

In this introduction I will first explain homoeotic mutants, and Goldschmidt's ideas. Secondly, I will examine how Goldschmidt related homoeotic mutants to evolution; and thirdly examine what is the real evidence about these mutants with regard to the question of origins.

The term *homoeosis* (from Greek *homoios*, "similar") denotes the replacement of one body part by another part usually considered to be homologous (of "similar" design); that is, a given organ or body segment develops structures which are characteristic of an organ or segment normally found elsewhere in the body. The term was coined by Bateson.[2] In the arthropods several different homoeotic phenomena are known, but those best known and studied are the homoeotic mutations in insects, particularly in the fruit fly, *Drosophila melanogaster.*

These mutations shift certain cells in "imaginal discs" (sac-like rudiments within the larva, consisting of thousands of embryonic cells, from which the adult cuticular structures arise during the pupal stage; see Figure 1 which is on the front cover) into a different developmental pathway, so that they form structures which are normally only formed by other discs or disc parts. For instance, in the mutant strain *aristapedia,* the arista (a feather-like appendage on the antenna) is replaced by a tarsus, i.e. the distal part of a leg (see Figure 2).

Many shifts of one disc to another have been discovered and will be concisely reviewed below, both as to genetic and to developmental aspects. Recently, I have extensively reviewed the phenomenon of homoeosis in *Advances in Genetics,*[3] after having worked on it for eight years as one of a few specialists in the field.

Figure 2. The homoeotic mutant *aristatarsia*, discovered by the author: arista partly (lower and right half) changed into tarsus (upper right: tarsal claw).

Professor Goldschmidt (1878-1958), an outstanding geneticist at the University of California in Berkeley, was one of the pioneers in the field of homoeosis on account of their supposed significance for his view of evolution. Recently, Macbeth again drew attention to this view when he wrote:

> It was in 1940, shortly after moving from Berlin to Berkeley, that Goldschmidt published his major work, *The Material Basis of Evolution.*[5] This touched off a controversy that has not yet entirely died down. The public hardly knew that anything was going on, but within the profession the Goldschmidt episode was a much greater event than the Scopes trial [the well-known judicial collision of creationism and evolutionism in

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> Tennessee, 1925]. The thrust and parry are worth reconstructing because they show how far we have moved from Darwin and how shaky the structure of evolutionary theory really is.[4]

In his book (and in later publications), Goldschmidt noted that the majority of species and genera appear suddenly in the fossil record, differing sharply from earlier groups, and that this apparent discontinuity becomes more common the higher the level, until it is virtually universal as regards phyla, classes, orders, and even families.

Secondly, he complained that at the same time the neo-Darwinian geneticists were talking more and more about little "point mutations" as the effective agents in causing change, and complained that their importance was said to vary inversely with their size. He declared himself to feel forced to give these "micromutations" up because they seemed to lead nowhere.

He pointed out that one may combine a thousand mutations into one fruit fly, which would be mathematically impossible, but it would still be a fruit fly. What was needed, suggested Goldschmidt, was something larger than point mutations; there must have been what he called "systemic mutations," something that shook up the whole system but still allowed it to survive and breed.

Of course, such big mutations would be so difficult to assimilate that it would most probably be fatal; but Goldschmidt suggested that it might succeed one time in a thousand to create a "hopeful monster," in the sense that divergencies gave "hope" for a glorious future. He listed 17 big changes, evolutionary novelties, which according to him (and creationists as well) could never be explained on a step-by-step basis.[6] The studies of microevolution might have a little value in explaining how the details were worked out after the macro-changes took place,[7] but in general, stated Goldschmidt, such studies would hardly have any value in the study of evolution as a whole.

Goldschmidt connected these statements with the supposition that the classical theory of the gene as an actually existing unit, lying on the chromosome like a bead in a string of beads, was no longer tenable.[8] He did not want to focus on genes and loci or even on chromosomes anymore but assumed something like "saltational mutations" to have occurred involving large portions of the genome and disturbing the whole system. Now, as valid as his objections to neo-Darwinism were, his ideas on the gene in general and on "systemic mutations" in particular were invalid. However, Goldschmidt seemed to make a strong case on some points, not the least by his studies on homoeotic mutants.

Goldschmidt on Homoeosis

Among the 17 inexplainable evolutionary novelties, i.e. the first appearance of new organs, Goldschmidt listed the segmentation of arthropods and vertebrates. In his 1940 book he observed:

> In two of the most important phyla of animals, in arthropods and vertebrates, one of the major features of evolution is the progressive specialization in segmentations of the body. In the primitive forms all segments are practically alike, each metamere containing a nephridium, a gonad, a muscle segment, a ganglion in arthropods, a neuromere in vertebrates, and an identical pair of appendages. In the course of evolution homomery is changed into a heteromery. In arthropods the appendages differentiate into mouth parts, legs, gonapophyses, disappear in some segments, change their function in others. In vertebrates the comparative anatomy of muscles, segmental nerves, and vertebral column demonstrates the changes from the considerable homomery of *Amphioxus* to all types of heteromery. *Among these evolutionary steps there are many of a type which preclude an evolution by slow accumulation of micromutations.* The mouth parts of a mosquito or of a bee, certainly derived from the primitive type of crustaceans and primitive insects, are an example in question: *gradations between generalized and specialized types would have died of starvation.*
>
> For a long time the phenomenon of *homoeosis* (called heteromorphosis by some authors) has been known as an occasional monstrosity in arthropods. The term signifies the appearance of a homologous appendage in a segment to which it does not belong. The classical example is the regeneration of an antenna after removal of the eyestalk in Decapods (Herbst). Homoeosis is now known to be produced also by simple mutation in *Drosophila,* an occurrence which permits an analysis in relation to our problem.[9] (Emphases added.)

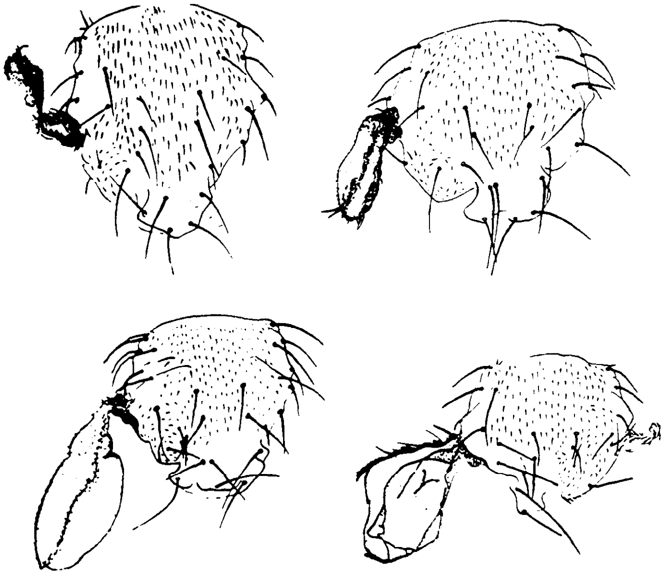

Figure 3. Picture from Goldschmidt's book, *The Material Basis of Evolution* (Reference 5, page 328), showing different conditions of wing transformation into a haltere in *Drosophila* mutant *tetraltera.* Only thorax and wings represented. Normal right wing not drawn where present. The picture is used here by permission of the Yale University Press.

Goldschmidt continued by mentioning the homoeotic mutants then known, and treating some research concerning larval development; obviously, after 35 years these data can be widely extended as is done below.

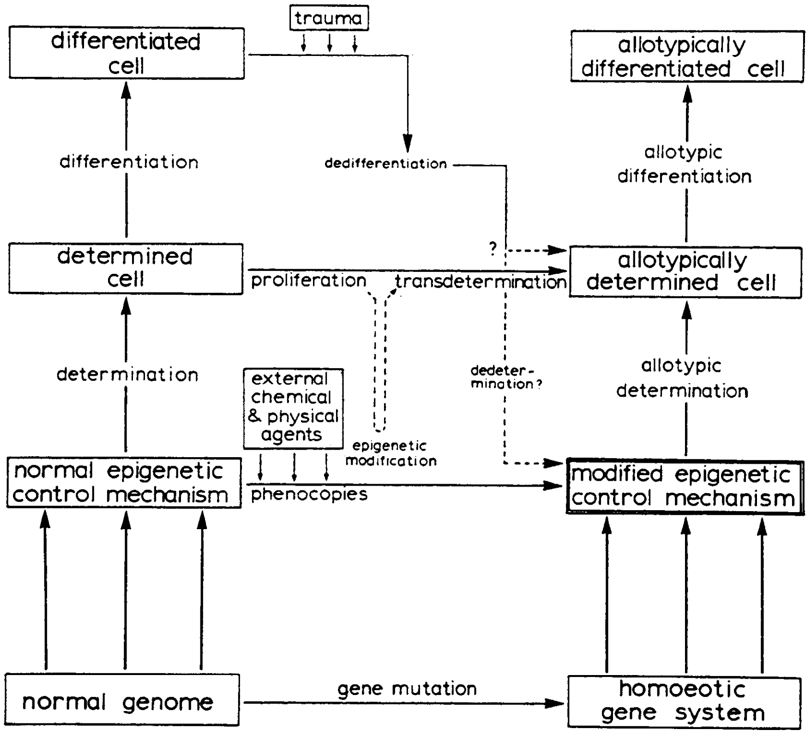

Figure 4. Diagram representing the hypothetical relationships between the different types of homoeosis arranged according to four developmental levels (bottom to top). The crucial element is the interference with the "epigenetic control mechanism" (regulating gene activities), the nature of which is not yet understood (cf. Figure 10). Allotypic = homoeotic.

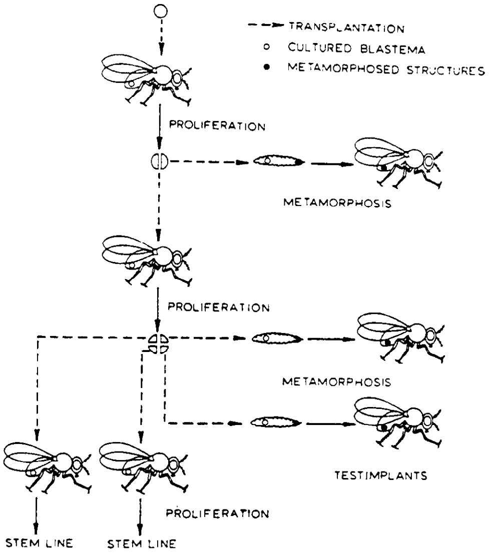

Figure 5. A fragment of an imaginal disc can be cultured in the abdomen of a fly or a larva. In the first case it strongly proliferates only, in the second case it undergoes metamorphosis along with the host. Tissues cultured in a fly can be divided again into fragments which can be further cultured in subsequent flies or can be transplanted as test implants into larvae.

In a following paper[10] in 1945, Goldschmidt described the homoeotic mutant *podoptera*, in which part of the wing is transformed into a leg-like structure with a complete series of transitions in different siblings in a strain (see Figure 3). He wrote in the discussion:

> In the forementioned book I discussed in detail how a decision [on the right genetic view of evolution] can be derived from genetics as well as from a proper evaluation of embryonic potentialities, and I showed how mutations acting upon certain developmental processes might accomplish in one step huge deviations. Homoeotic mutants served as one of the examples to furnish proof of such ideas. The homoeotic mutant analyzed in this paper is a still better example for such a discussion. Here we have a clear-cut case of an organ characterizing a class [viz. the winged insects] being able to mutate in one step into another more primitive organ. We have every reason to believe that the opposite also happens, namely, mutation of leg into wing, which occurs as occasional freaks. There exists also one little-known mutant in Drosophila in which it is claimed that an antenna (itself capable of mutating to a leg) transforms into a wing-like structure. It would certainly be difficult [but not impossible . . . W.J.O.] to evade the conclusion that the first wing must have appeared as a mutant of a parapodium containing a trisegmented leg-like appendage [which, claimed Goldschmidt, is found back in the trisegmented "costa" at the proximo-anterior wing border].[11]

Other statements by Goldschmidt will be considered below, after a review of present knowledge of homoeotic phenomena.

Types of Homoeotic Transformation

Within the arthropods four types of homoeosis are known, occurring on four different developmental levels (see Figure 4):

(a) *Homoeotic mutations* involve a change in one or more genes, or in chromosomal arrangement, leading to the formation of altered gene products which effectuate shifts in cell differentiation and pattern formation. They have been found in several insect genera.

(b) *Homoeotic phenocopies;* this term refers to organs or flies which are phenotypic copies of known homoeotic mutants and are caused by external chemical and physical factors which apparently interfere with the relevant gene products or their metabolites during development but leave the genes intact. The factors involved (chemicals in the food, vapors, cold and heat shocks, X and UV irradiation, neutron bombardment) have been applied to embryonic or larval stages of *Drosophila*.

(c) *Transdetermination;* this is homoeotic alteration occurring in imaginal-disc cells that were already "determined" for a certain developmental pathway. It can be brought about by culturing imaginal-disc fragments (dissected from a mature larva) for a sufficiently long period within adult hosts where they cannot undergo metamorphosis (see Figure 5). This culturing usually leads to a gradual increase in proliferation rate, but even after years of serial transplantation (from one host to another) the cells maintain the original embryonic character.

When pieces of these cultured fragments are transplanted back into a larval host they undergo metamorphosis along with the host and nearly always develop into adult cuticular structures. Such test pieces usually produce the structures for which they were originally determined, but test pieces from later transfer stages may, probably as a consequence of the extensive and rapid proliferation, differentiate into homoeotic structures, i.e., normally only formed by other discs.

(d) *Homoeotic regeneration* has been described in various adult arthropods outside the insects. In this case an extirpated appendage is replaced by a serially homologous one. I quoted already Goldschmidt mentioning the regeneration of an antenna instead of a removed eyestalk in Decapods. Occasionally spontaneous homoeotic aberrations (either embryonic or regenerative in origin) have also been encountered.

The interesting factor in homoeotic regeneration is that the cells involved are already "differentiated" (i.e., in their terminal developmental stage). It is obvious, therefore, that the cells at the wound surface first have to undergo "de-differentiation" (a return to a more embryonic state) and then will proliferate, at the same time undergoing a kind of transdetermination.

It is interesting to note, by the way, that phenomena similar to homoeosis may occur in other phyla too. Morphological and physiological alteration of "determined" or fully "differentiated" cells during embryogenesis and during regeneration is a well-known phenomenon in several animals, and is usually called *metaplasia.* For those familiar with embryology I may note that even phenomena such as embryonic induction and regulation, and even neoplasia (cancer), can be related to metaplasia and homoeosis. I refer again to my extensive 1975 review article (Reference 3).

Types of Homoeotic Mutation

By far the most homoeotic mutations have been found in *Drosophila melanogaster,* but I will also mention below some other insects. I will consider several examples of mutations producing, from a given imaginal disc, structures normally formed by other discs. In 1940 Goldschmidt knew only of five types of homoeotic mutation, but at present several dozens have been identified. They are known for all imaginal discs (i.e., the labial, eye-antennal, prothorax, wing, haltere, leg, and genital discs), although not all homoeotic transformations known to be possible from transdetermination experiments have been encountered.

Some reasons for this might be, e.g., that homoeotic mutations in the genital disc would prevent reproduction and mutations producing wing structures from the leg disc would impede emergence from the puparium. Indeed, several of such homoeotic mutants have been encountered by allowing imaginal discs from lethal mutants to metamorphose in host animals.[12]

Homoeotic transformation is a highly specific process, as is strikingly evident in the antenna: (a) *aristapedia* (ss^a) changes the arista into the distal part of the tarsus; (b) *tumorous-head* (*tuh*) changes the arista and part of the "third antennal segment" (ant. III) into a complete tarsus; (c) *Antennapedia* (*Antp*) changes the arista and the whole ant. III into a tarsus, tibia, and femur; (d) *lethal(4)29* changes ant. I and ant. II into a coxa and trochanter (i.e., more proximal leg segments); (e) while *Nasobemia* (*Ns*) moreover changes the cuticle around the antennal basis into a sternopleura (i.e., the thoracic structure around a leg basis) (Figure 6).

All these transformations imply that each antennal part corresponds to a specific leg part. *Antennopedix* (*Apx*) is also able to form a complete midleg, but the arista is usually not entirely replaced. All homoeotic changes in the antenna are toward leg formation, with the striking exception of the mutant producing a wing-like structure mentioned by Goldschmidt (see quote above).

The *tuh* stock mentioned exhibits also abdominal tergites instead of eye facets, and anal plates, clasper teeth, and antennal and leg outgrowths instead of rostral cuticle. Such pleiotropic effects are exceptional among homoeotic mutants.

Other homoeotic head mutants, those of the *ophthalmoptera* type, carry wing outgrowths in reduced eyes (Figure 6); my Ph.D.-thesis[13] involved a study of such mutants. Another head mutant is *proboscipedia* (*pb*) in which the mouth parts are partly transformed into either tarsus- or antenna-like structures. Interestingly, this modification resembles the biting type in certain lower insects, although the homoeotic outgrowths impede feeding—a first indication that homoeotic mutants (a) may as well lead, not to higher but, to lower organismal types of complexity ("evolutionary levels," to use Goldschmidt's language), and (b) are basically destructive in providing for the organism organs it cannot use and at the same time depriving the organism of original, often indispensable organs.

The only rigid leg transformation known was encountered by Waddington in some combined strains of leg mutants and involved a leg terminating in an arista-like spike instead of the usual tarsal claws. Besides that, a number of other mutations partly or completely change the midleg and hindleg into a foreleg, expressed particularly in a shortening of the basitarsus, transformed bristle and hair patterns, and the presence of sex combs on posterior legs (normally only on forelegs) in the males.

Now with regard to the dorsal thoracic structures, there is a remarkable mutant in *Hexaptera* (*Hx*) which, besides an enlargement of the whole dorsal part of the prothorax (i.e., the first thoracic, appendage-less, segment), produces homoeotic appendages on it. They alternatively consist of wing membrane, resemble a haltere (i.e., the dorsal paired club-like flight instruments of the metathorax or third thoracic sgement), or are distinct though irregular legs. Sometimes an appendage is proximally leg-like and distally

Figure 6. Two homoeotic mutants expressed in one head: *ophthalmoptera:* eye area producing wing-like outgrowths (upper right), and *Nasobemia:* antennae changed into legs (middle right and lower middle).

wing-like, or a dorsal prothorax may even bear two or three appendages, e.g. two legs and one wing.

On the dorsal part of the mesothorax (i.e., the second thoracic segment) there are wings, which may be genetically replaced by appendages resembling halteres or legs. It is these mutants of the *podoptera* (*pod*) type which were particularly studied by Goldschmidt.[14, 15] (See also references 1, 5 and 10) I mentioned already that the intermediate stages between wing and haltere form a continuous series; interestingly, this series is entirely similar to the same series in certain other mutants which, reversely, change halteres into wing-like appendages in all degrees. Goldschmidt noted further that the (tripartite) wing costa seems to be homologous to the distal leg (coxa, femur, and tibia) and that as the wing diminishes in size thoracic duplications increase in number, suggesting that the latter replaces wing parts.

Next, consideration should be given to the so-called *bithorax* complex, a series of (at least) seven pseudoalleles changing dorsal and ventral anterior and/or posterior parts of certain body segments into the corresponding parts of other body segments. Only *Contrabithorax* (*Cbx*) affects the mesothorax (including the wings). Three others change the metathorax (including the halteres)—*bithorax* (*bx*), the anterior portion (Figure 7), and *bithoraxoid (bxd)* and *postbithorax* (*pbx*) the posterior portion—into the corresponding mesothoracic structures. *Ultrabithorax (Ubx)* exhibits a combination of the phenotypic effects of these three recessive mutations.

Contrabithoraxoid (Cbxd) exceptionally produces a partial transformation of the metathorax into the

Figure 7. The homoeotic mutant *bithorax:* anterior methathorax and haltere halves changed into anterior mesothorax and wing halves.

first abdominal segment (abd.I) next to it, so that the fly occasionally bears five or even four legs instead of six. Three pseudoalleles interestingly affect the abd.I directly: *Ultraabdominal* (*Uab*) changes it into an abd.II, and *Ubx* and *bxd* transform it into thoracic structures. It is interesting that some mutants such as *bx* and *bxd* affect both the dorsal and ventral segment half: *bxd* sometimes produces both a (dorsal) pair of haltere-like appendages and a (ventral) fourth pair of legs in the abd.I.

Finally as to the genital disc, a lethal mutant is known[12] transforming genital into tarsal and antennal structures. Besides that, also the "sex-transforming" mutants could be considered as homoeotic. They determine genital discs which are chromosomally female to produce male organs, and conversely, and correspondingly affect the development of the gonad primordia.

Homoeotic mutations in species other than *Drosophila melanogaster* are little known. Examples have been encountered especially among other *Drosophila* species, where they are very similar to the corresponding ones in *D. melanogaster*. The same holds for the house-fly, *Musca domestica*. Next are the mosquitos, in which some mutants of the *pb*-type have been found (see above); such mutants may be female-sterile because females cannot pierce skin and hence cannot obtain the blood needed for egg production,[16] which would not be very helpful in evolution.

The *E*-allelic group in the silkworm *Bombyx mori* is very interesting.[17] The first two abdominal segments in the caterpillar normally have no legs; some *E* alleles, however, produce larval thoracic legs on these abd.I and II, some produce thoracic legs on all segments, and one produces thoracic legs on abd.I and abdominal legs on abd.II. In the flour beetle genus *Tribolium* a mutant of the *Antp*-type and one of the *pb*-type is known.

Finally, the most primitive insect known (to me) to exhibit a homoeotic trait is the German cockroach, *Blattella germanica*.[18] This X-ray induced, dominant mutation is *Pro-wings*, characterized by lateroposteriorly directed enlargements of the pronotum which resemble a pair of diminutive wings.

Ross points out that the occurrence of "pro-wings" in one of the most primitive (heterometabolous) pterygotes (winged insects) is of special interest in connection with the presence of paranotal lobes or wing flaps on the prothorax of the "oldest" (in uniformitarian terms) known fossil pterygotes. Here again therefore, if evolution were really involved, there would apparently be a case for degeneration rather than one for "improvement." The same holds for an example enthusiastically mentioned by Goldschmidt,[19] namely the minute rudimentary wings in the very aberrant termitophile fly *Termitoxenia,* which would be identical to the homoeotic wings intermediate between halteres and wings both in "wing to haltere" and in "haltere to wing" mutants in *Drosophila.* Again, if this has anything to do with evolution it points largely to degeneration.

Genetic Properties

Most homoeotic mutants in the fruit fly seem to be point mutations, although they are often connected with chromosomal aberrations. It is striking, however, that a relatively large number of them, at least 11, are all located in the same region of the right arm of the third chromosome, between loci 47± and 58.8. Goldschmidt[20] mentioned this fact as supporting his hypothesis that there are no "genes" but that the chromosomes themselves act as units in the genetic control of normal development. But at that time (1938) homoeotic mutations were known in this 3R-region only; now they are known to be distributed over all four chromosomes, often in lone positions.

Denell[21] suggested that the unusual clustering of genes of similar (viz., leg, and antenna-changing) function around the locus 47-48 may be due to their being derived from a single "ancestor gene" through gene duplication and subsequent diversification of function; in addition, such clustering might be necessary to make possible their coordinate control.

The chromosome region concerned has frequently been found to be the end or the beginning of a chromosomal inversion involving various homoeotic alleles. Other homoeotic mutations appear to be involved in chromosomal translocations. Again other homoeotic mutations are combined in a pseudoallelic series like the *bx* complex.

The *podoptera* group is genetically the most complicated one and was most extensively studied by Goldschmidt. (See reference 15) It embraces a number of different, very variable hereditary strains in which the wings are transformed into leg-like, three-jointed appendages. In no case is this effectuated by a single mutation, however. Four types are distinguished, all multifactorial, with factors on all chromosomes and each with a major factor on the second chromosome; moreover, in most cases the *pod* effect is dependent on heterochromatic chromosome regions.

Mittwoch[22] has suggested an interesting parallel between the *pod* effect in *Drosophila* and sex differentiation in mammals. Both cases involve an undifferentiated rudiment to which two possible developmental routes are open: from the wing imaginal disc either a wing or a (homoeotic) leg is formed, while the mammalian gonad anlage produces either a testis or an ovary, heterochromatin playing a crucial role in either case. Certainly, no evolutionist would suggest an evolutionary relationship here; on the contrary, only an interesting "developmental convergence" can be claimed.

A next genetic feature of homoeotic mutants is that frequently their penetrance and expressivity are strongly influenced by modifying genes: "suppressors" or "enhancers." In some cases (e.g., *tuh*) the homoeotic effect even entirely depends on two seemingly unrelated mutations. In the group of *opht* effects, the homoeotic transformation always requires an eye-reducing gene in addition to the actual homoeotic factors which produce the wing outgrowths in the eye area. (See reference 13)

Interestingly, homoeotic organs may be secondarily altered by other homoeotic genes; in such cases the effect of the "secondary" gene is superimposed on that of the "primary" gene. For instance, at low temperatures *pb* changes the mouth parts into arista; ss^a (changing the arista into a tarsus) is also associated with the arista-producing effect of *pb* towards tarsus-production[23] (see Figure 8). In *Ns/Pc* flies, *Ns* changes the entire antenna into a complete midleg, while *Pc* changes this midleg immediately into a foreleg.[24] For other examples see my 1975 review.

Some homoeotic mutations which drastically influence the segmentation pattern and polarity of the fly must exert primary effects at a very early embryonic stage, namely when the determination of imaginal disc precursor cells appears to occur (the stage of "blastoderm" formation in the 2½ hrs. old embryo). This is supported by the fact that a drastic mutation such as *bx* can be phenocopied by ether treatment and heat shocks at this early stage.

This leads me to expect that there will be homoeotic mutants which exhibit so-called "maternal effects," which means that the homoeotic effect depends on the genotype of the mother, namely the genotype of the egg, not that of the zygote nucleus. However, such mutants are very rare, probably because they usually would lead to lethal development.

I should cite one example of a homoeotic maternal-effect mutant, one which is related to the *bx* phenocopies just mentioned and has supposed evolutionary significance. Professor Waddington,[25] another pioneer in homoeosis, subjected 2½-3½ hrs. old wild-type eggs to ether vapor and selected the flies developed from these eggs for the tendency to produce *bx* phenocopies.

In two different selection lines, flies with slightly enlarged halteres gradually appeared among the untreated individuals and were found to contain an allele of *Ubx,* possibly due to independent chance mutations. In one of the lines in addition a much more extreme *bx* phenotype, due to several genes, appeared in high frequency among the untreated individuals.

These pseudo-Lamarckian acquirements are beautiful examples of "genetic assimilation," the process by which the genotype takes over the role of a certain

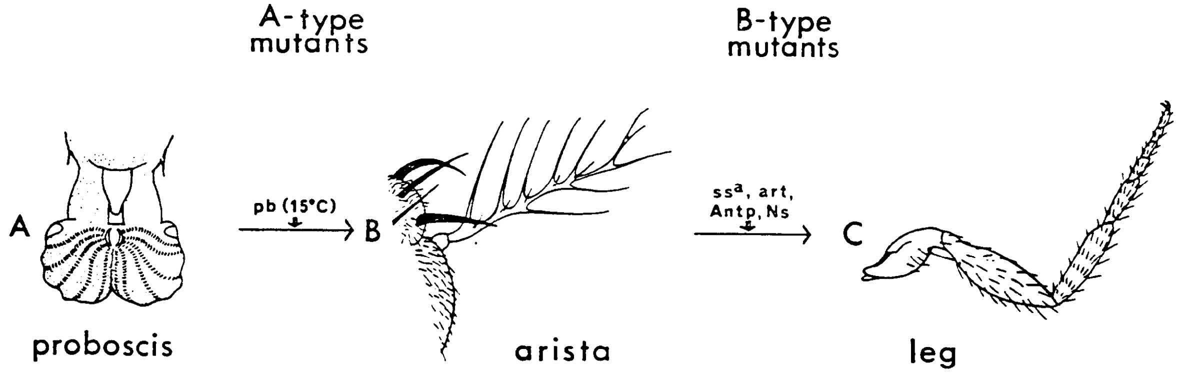

Figure 8. Diagram of a "transformation series" controlled by homoeotic genes. The A-type mutant *proboscipedia (pb)* changes, at low temperature, the mouth parts into aristae, while the B-type mutants *aristapedia (ss^a)*, *aristatarsia (art)*, *Antennapedia (Antp)* or *Nasobemia (Ns)*, which normally change an arista into tarsus, in combination with *pb* directly produce tarsi out of the mouth parts.

environmental factor in producing a given phenotype. The "assimilated *bx*" stock is known as *He**. Its phenotype is partially due to a number of genes acting directly on the individuals containing them, and partly to a recessive X-chromosome condition which causes a maternal effect. Probably a gene or group of genes around locus 33 is involved. Waddington suggested that the condition had arisen by mutation during the course of selection but rightly emphasized that the possibility cannot be excluded that it was present in very low frequency in the initial population.

Developmental Properties

One of the most elegant tools in the developmental analysis of homoeotic mutants involves the technique of genetic mosaics. I consider here two types of mosaics:

(1) Genetically marked tissue patches on flies; such patches are cell clones arising as a result of either (a) gynandromorphism due to the elimination of one X chromosome during a cell division in the early development of a female, leading to an XO (i.e., male) cell clone in further development; or (b) somatic crossing-over (SCO); this can be induced at any stage of development particularly by means of X, UV, or γ irradiation; when the appropriate genetic "markers" are used SCO in any cell will lead to a clone of phenotypically different cells derived from the affected mother-cell. These cells are hemi- or homozygous whereas the background tissue is heterozygous for the recessive marker allele(s) used.

The technique can be used for two purposes. First, the homoeotic mutations are used to mark induced clones in order to study the developmental behavior of small homoeotic patches in otherwise normal organs. It has been shown that such patches invariably develop autonomously, i.e., according to their homoeotic genotype, unless SCO is induced at very late stages when the cells probably are definitively determined for wild-type development; see further my 1975 review.

Secondly, the technique has been used to study the morphogenesis of homoeotic organs by means of genetic markers affecting body color or chaetal color or shape. It was used particularly by Postlethwait and Schneiderman[26] in their study of *Antennapedia*. They described an experiment to establish whether the homoeotic area in the antenna is the progeny of a single cell or whether the homoeotic transformation occurs in a population of cells.

If marked patches are induced prior to the "determinative" event, then in the former case some antennae would have their homoeotic part entirely included within the induced patch, whereas in the second case in some antennae the marked patch would overlap the antennal and the homoeotic part against an unmarked overlapping background. (If the patches are induced after determination, they would in both cases be confined to either antennal or homoeotic areas.)

In this way it could be established that, firstly, the homoeotic determination occurs in a population of about ten cells and, secondly, that this takes place in the early third larval instar. Moreover, it seems that upon this determination the presumptive leg cells show an increased growth rate more characteristic for growth in the leg disc, whereas the presumptive antennal cells maintain a growth pattern more typical of the antennal disc.

(2) In some homoeotic mutants, which produce their effects at varying expressivities, the affected organ may form a "phenotypic mosaic" consisting partly of normal, partly of homoeotic tissue. Postlethwait and Schneiderman discovered in *Antp* antennae that very specific antennal parts were replaced by very specific leg parts only. They suggested that the two cell types respond to an identical set of "positional cues" which are "interpreted" by the developing cells either in a "leg-like" or an "antenna-like" way, depending on whether the homoeotic mutant comes to expression in a given cell or not.

I conducted a similar study[27] in homoeotic haltere mutants. Using *bx* and *pbx* has the advantage that only part (viz., the anterior or the posterior part, respectively) of the haltere is transformed, so that at each proximodistal level adjacent haltere and wing

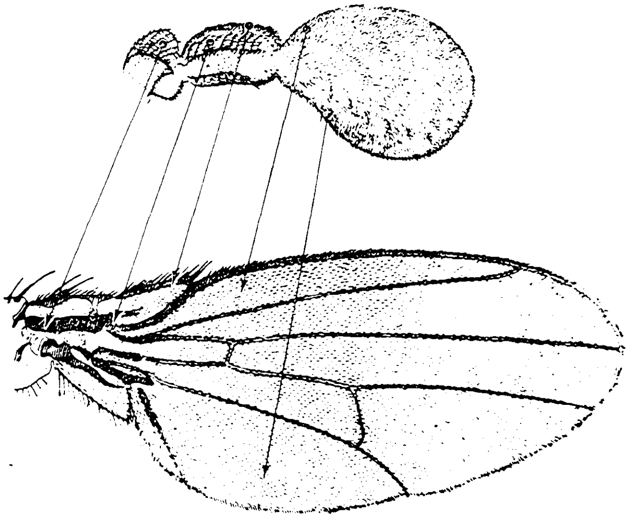

Figure 9. The homology between haltere (above) and wing structures (below) as determined by site-specific transformations in homoeotic halteres of *bithorax* and *postbithorax*. The segmented structure can be fairly clearly found back in the wing. The groups of sensilla correspond accurately.

structures can be compared (see Figure 9), while the borderline between them may vary along the anteroposterior axis. Close examination of *bx* and *pbx* halteres made it possible to establish exact homologies between certain haltere and wing structures (and even small sensilla groups).

I mentioned that the homoeotic determination in the *Antp* antennal disc must occur in the early third larval instar. Other techniques to establish the time of determination are:

(1) *The phenocritical phase.* This is the time at which the phenotype of a mutant animal begins to deviate from that of the wild-type; obviously this cannot occur before the time of gene action. For instance, I studied the outgrowths in *opht* eye discs which produce the wing bulges in the adult eyes, and found that they are not visible until shortly before the middle of the third larval instar. (See reference 13)

(2) *The phenocopy-sensitive period.* Some phenocopies are produced at specific developmental stages only and Goldschmidt suggested that therefore they are indicative of the time of determination. (See reference 20) One must bear in mind, however, that the nature of the phenocopying agents is quite unspecific and the mechanism of action is unknown.

(3) *The temperature-sensitive period (t.s.p).* The penetrance and expressivity of homoeotic mutants usually are very sensitive to changes in temperature. Heat and cold shocks usually are only effective during certain developmental stages which are therefore thought to indicate the time of determination. This t.s.p. may be at any stage but usually occurs in the third instar. Some mutants are heat-sensitive, others are cold-sensitive, and *pb* is both: it changes the mouthparts into aristae at low, and into tarsi at high temperature.

Grigliatti and Suzuki[28] made an interesting observation in their t.s.p. study in ss^{a40a}. "Shifts up" (i.e., from low to high temperature) at successive stages during the t.s.p. led to aristae having homoeotic proximal parts which gradually increased distally while the size of the remaining arista decreased.

"Shifts down" at successive stages led to the reverse pattern, but always the proximal part was homoeotic and the distal part normal arista. Presumably, the size of the homoeotic part of the arista is proportional to the fraction of the t.s.p. spent at low temperature.

Apart from temperature, few other environmental factors have been examined for their effects on homoeosis. It is peculiar that very large effects may be exerted by very trivial factors like the supply of fresh yeast to the larvae, simple aging of the larval culture, and the age of the mothers. (See reference 13) Chemicals added to the food may either interfere directly with homoeotic development or prolong the larval period and thus affect the growth pattern of homoeotic primordia. (See reference 13)

A more direct influence upon disc growth can be achieved by direct treatment of the discs followed by *in vivo* culturing. I have bathed homoeotic discs in various colchicine solutions and then transplanted them into host larvae, where they undergo metamorphosis along with the host. According to the results, colchicine, which is best known for the fact that it will arrest mitosis, may under certain circumstances exert a mitosis-enhancing effect, as was found by many other authors (See my 1975 review).

I also used the transplantation technique to construct "fate maps" of the wild-type and *opht* eye discs by means of disc fragmentation. (See reference 13) I showed the presumptive eye area to be located in the flat part of the disc, surrounded by head cuticle primordia, and probably to be entirely capable of wing formation.

I also cultured very young eye discs in adult, wild-type hosts for some weeks (where they terminate larval development) and then transplanted them back into full-grown wild-type larvae. (See reference 13) During metamorphosis the discs produced homoeotic wing tissue. This could not have been induced in the disc by the larval environment (of which it was deprived). Therefore, I concluded that it developed autonomously.

Similar experiments had been completed by other authors with the same results, although not at such an early stage. It has been shown that even the overall development of normal imaginal discs is independent of the larval internal environment. The discs autonomously determine an intrinsic developmental program depending on a phase of proliferation, no matter whether this takes place *in situ*, in a metamorphosing larval host, in an adult host, or *in vitro*. This is an important point in view of Goldschmidt's ideas of homoeosis to be discussed below.

Finally, I mention some examples of homoeotic regeneration. Pantelouris and Waddington[29] extirpated whole wild-type and *He** wing discs to study the regulative response of the animal. They suggested that in some cases the remaining wing disc or the homoeotic haltere disc on the operated side, respectively, partially regenerated the missing disc. It seems however, that in cases of apparent regeneration the wing disc was not completely removed and that the small remaining disc fragment, through cell proliferation, had produced the regenerated structure.[30]

In fact, several researchers[31] have shown that certain disc fragments can indeed regenerate missing structures, although in a polarized way: complementary disc fragments, after similar additional proliferation, only duplicate, in mirror-image fashion, the primordia they contain.

For instance, when the (normally attached) eye and antennal discs are separated, cultured in adult hosts, and then injected into mature larvae, eye discs regenerate the antennal disc whereas antennal discs only duplicate the same tissue. This holds for both wild-type and homoeotic *(ss^a)* discs: ss^a eye discs may, through growth, regenerate antennal structures including homoeotic tarsi, while ss^a antennal discs may produce homoeotic tarsi in duplicate. If discs of the temperature-sensitive mutant ss^{a40a} are isolated and cultured after the t.s.p., the phenotype of an antenna, arisen by regeneration or duplication, turns out to depend entirely on the temperature of the *in vivo* culture and therefore to be independent of the original t.s.p.[32]

Hypotheses of Homoeosis

(1) *Evocators.* The first hypothesis of homoeosis was proposed by Goldschmidt in his 1938 and 1940 books, mainly on the basis of a developmental timetable given for the wild-type and ss^a leg and antennal discs already in 1929. He suggested that at different times during larval development different "evocators" (inducing substances) are released, which determine those discs which have become "ripe" (competent for "determination") just at the time of release of each evocator.

For instance, at a certain time the leg discs would have become "ripe"; at that time a tarsus evocator would be released into the larval body fluid, which would determine the leg discs for tarsus development. Other discs are not determined by the tarsus evocator, either because they are already determined or because they are not yet "ripe."

In the ss^a mutant the growth rate of the antennal disc would be changed in such a way that the disc now becomes competent at the time of release, not of the arista evocator but of the tarsus evocator, so that the arista primordium does not acquire arista but tarsus quality.

This hypothesis was seriously attacked by Marguerite Vogt.[33] First, her own studies on the ss^a discs disproved the old time-table of 1929 and therefore removed the main foundation of Goldschmidt's hypothesis. Secondly, she rightly argued that the observation that 2½ day-old ss^a antennal discs implanted into normal larvae still produced homoeotic legs would constitute no argument for accelerated disc development if the latter were autonomous—which it indeed proves to be. Goldschmidt later recognized the validity of Vogt's arguments. (See reference 15) All the evidence now available is contradictory to the presence of "evocators" in the larval body fluid which would diffuse into and determine the discs. I have conclusively shown by my own experiments in 1970 that homoeotic discs can develop autonomously in wild-type host larvae.

(2) *Switch genes.* It is more plausible to look for the cause of homoeotic transformations in the genetic regulation mechanisms **within** the discs. This is what Waddington[34] did. He pointed out, for instance, that in the case of ss^a the arista primordium within the antennal disc cell growth occurs along two distinct alternatives, the "arista developmental pathway" or the "tarsus developmental pathway," each controlled by a large number of "morphological" genes (arista genes and tarsus genes, respectively).

These pathways never merge but are strictly "canalized"; that is, their respective genes constitute coherent genetic systems. In the wild-type arista primordium the subsystem of arista genes is "turned on," while the subsystem of tarsus genes is "turned on" in the wild-type tarsus anlage of the leg disc.

Now Waddington suggested that the homoeotic genes act as "switch genes" or "key genes" which in a given disc or disc part turn on a different genetic subsystem, thus switching development into another developmental pathway. The function of the wild-type allele of a homoeotic gene like ss^a might be that of repressing developmental pathways typical of homologous organs.[35] A collateral problem would be why the ss^a gene (either normal or mutant) is active in the arista primordium only (see below).

A similar but somewhat more tangible model to suggest an explanation for these problems has recently been designed by Kiger[36] for the *bx* complex locus. His ingenious though speculative model is similar to the famous general model of genetic regulation by Britten and Davidson.[37]

He suggested that morphological genes belonging to one subsystem are each controlled by a contiguous "expressor gene"; all the expressor genes of one subsystem would produce identical expressors, which as a class would be subject to the same control, namely by the homoeotic "key gene." This gene would produce a protein with different functional states, depending on the genotype, so that it can selectively activate different expressor classes. I will not go into this further (See my 1975 review), but refer to Figure 10.

(3) *Positional information.* This concept was formulated by Professor Lewis Wolpert.[38] He has suggested that there may be a universal mechanism whereby genetic information is translated into spatial differentiation patterns. This mechanism would be based on the specification of the position of a cell with respect to one or more "reference points" in a developing system. This specification of position yields "positional information," which could be thought of as a scalar quantity, even shaped as a simple gradient of some physical or chemical factor.

I have formulated some rules[39] in such terms to account for duplication and regeneration in cultured disc fragments (See also reference 31). Imaginal discs are thought to differ not in the specification but in the

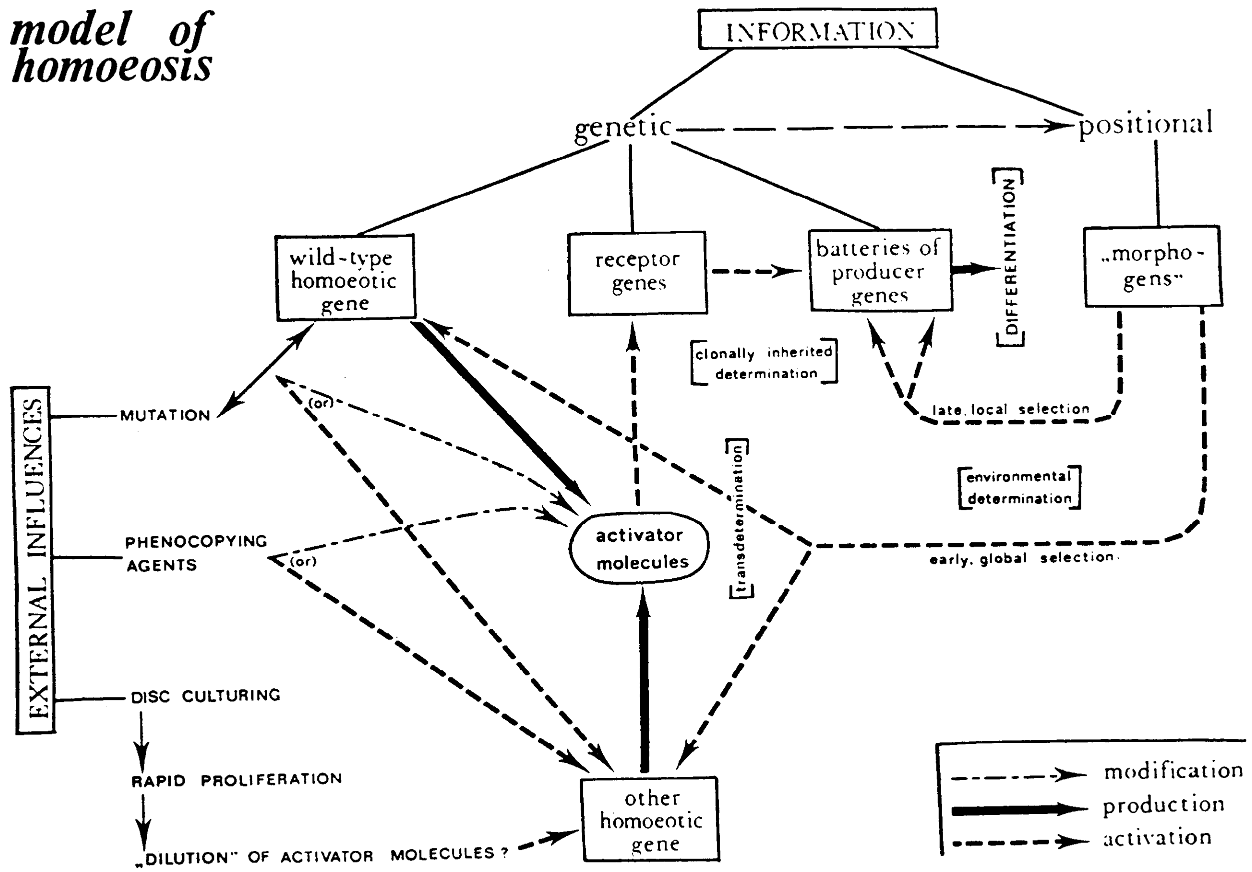

Figure 10. Diagram unifying several views on homoeosis. Developmental information is thought to be at least of two types: (a) genetic information, including the homoeotic genes ("integrators"), "receptor genes"; and batteries of "producer genes"; (b) positional information thought to be provided by "morphogens" of unknown nature.

At an early stage positional information (also under control of the genome) may differentially activate the integrators in the various imaginal discs or disc parts. An integrator may produce activator-RNA molecules which activate a specific type of receptor gene; each receptor gene controls an adjacent producer gene; all producer genes controlled by one type of receptor gene form a battery.

Batteries may either correspond to sets of "morphological" genes together producing a given structure, or to "bistable control circuits" overlapping several imaginal discs. Activation of certain batteries leads to a clonally inherited type of cellular determination, whereas the determination of the ultimate supracellular differentiated pattern is of an environmental type thought to be due to positional information. External influences produce homoeotic phenomena.

Both mutation of a homoeotic gene and phenocopying agents may modify the activator molecules and/or lead to activation of a different wild-type homoeotic gene by some sort of negative regulation. Imaginal disc culturing usually leads to rapid cell proliferation by which hypothetical "determination carriers" (activator molecules?) might be "diluted"; this might lead similarly to the activation of a different homoeotic gene.

interpretation of positional information; homoeotic mutants are therefore thought to alter the latter, not the former.

One of the most elegant illustrations of the putative significance of the concept seems to be provided by the phenotypic mosaics studied by others (See reference 26) for *Antp* and by myself (See reference 27) for *bx* and *pbx*. The precise site-specific nature of the homoeotic structures seems to imply that leg and wing cells respond to the same set of positional values as do antennal and haltere cells, respectively; the interpretation of these values would then depend on the homoeotic genotype.

In addition, it is possible that the presumptive imaginal discs are specified by positional information in the very early embryo.[39] This implies that the discs would be provided each with a specific mode of interpretation of the identical set of positional values within them, and this on the basis of their position in the early embryo.

(4) *Control circuits.* Stuart Kauffman[40] has recently proposed a new model for genetic regulation of development in higher organisms, which he then applied in particular to homoeotic phenomena. He observed that for regulated genes and processes at least one "control variable" has a state which determines the outcome of the process regardless of the states of other regulatory variables. Regulated genes always seem to be governed especially by such "canalizing functions" (i.e., capable of determining the behavior of the regulated process).

Secondly, Kauffman introduced "forcing loops": gene A "forces" gene B if A is canalized and in that state canalizes B. In turn B may force C, and so on, while the last element of the chain may have a forcing feedback on A. Such a "forcing loop" maximally has two steady states, a stable one insensitive to external regulatory events and having each element in its canalized state, and a sensitive, metastable one having each element in its non-canalized state.

This hypothesis has been extensively worked out for genetic regulation in bacteriophages but it is not self-evident that it applies to eukaryotes. It is particularly the determinative states of mature imaginal discs, however, that might possibly be due to "control circuits" assuming stationary states, somewhat as Waddington postulated alternative developmental pathways, and Wolpert alternative interpretations of positional information.

Kauffman suggested that each disc is characterized by a specific combination of control circuit states, and argues that, in transdeterminative events (see above) and in homoeotic mutants, one control circuit changes from the less stable to the more stable state, or sometimes perhaps *vice versa.* He adduces quite a few corroborating experiments which I cannot go into here (See my 1975 review).

Although the model is highly speculative, it is stimulating because it indicates new ways of research on homoeosis, such as determining how many control circuits there are, searching for pleiotropic effects in homoeotic mutants, and testing the relative transdetermination frequencies in them.*

Homoeosis and Evolution

Now that the present knowledge of homoeotic phenomena has been summarized, Goldschmidt's view of evolution can be evaluated as far as it concerns homoeotic mutants. I feel that two interesting conclusions can be drawn.

(a) Goldschmidt's criticism of neo-Darwinism as an explanation for macroevolution is still as valid and as destructive as it was in his days. Absolutely no newer data have been collected that could be used to counter his strong objections to the synthetic theory.

(b) However, his hypothesis of homoeosis used as strong evidence for his own alternative view of evolution has turned out to be as invalid as neo-Darwinism. Both his assumption of the non-genetic basis of homoeosis and that of evocators released in the larval body fluid at various times have been discarded. Moreover, I will show that according to present knowledge of the action of homoeotic mutants, they could not have any role in a supposed macroevolution.

Other critics of classical neo-Darwinism today seem to be in the same position. For a number of years the so-called "neutralist theory," virtually related to some older ideas of Goldschmidt (although this is hardly recognized), has been propounded by geneticists such as Kimura, King, Jukes, and Ohta.[41] These theorists criticize the view that natural selection is the only or basic force in evolution in much the same way as Goldschmidt did or as creationists do. They propose an alternative theory, however (stating that many mutations are neutral from the standpoint of natural selection and that gene frequencies in populations change by "random genetic drift" in limited populations), which appears to be at least as untenable as the classical synthetic theory as an adequate explanation even for microevolution.[42] If geneticists do not agree on mechanisms of microevolution they are even much farther from any genetic theory that could account for macroevolution.

The cause of all this confusion is the unfounded presupposition that evolution has taken place at all.[43] Take the example of the argument from comparative anatomy, so eagerly used by Goldschmidt. Many creationists have already pointed out that similarities ("homologous patterns") do not necessarily indicate common ancestry; they might equally well point to a common design and a common Designer.

For those who accept the creation model, a study of homoeotic phenomena more and more reveals an inconceivably complicated and impressively well-ordered ground-plan which the Creator has provided in such complex animals as the insects. Read, for instance, the 1973 and 1974 papers by Kauffman, and, if his model be valid, try to conceive how such an intricate, sensitive, compliant, and neatly regulating system could have even developed by natural selection of random mutations.

Then compare this with what is now labelled by some as the "naive" view Goldschmidt held regarding the action of homoeotic mutations. Of course, he knew little of them in his day, but what I mean to say is that evolution always seems to be more conceivable the less is known of the extreme complexity of the living systems concerned. Moreover, such systems may genetically *vary* indeed—but this is altogether a different problem from the question of how they did *originate.*

I will come back to this problem in a moment but first I must turn to a second pillar of the evolutionary doctrine, namely paleontology. Just consider the complex animals involved—the insects. Morris recently wrote:

> If the evolutionary origin of the higher animals is obscure, the origin of insects is completely blank. Insects occur in fantastic number and variety, but there is no fossil clue to their development from some kind of evolutionary ancestor. . . . The most remarkable feature about such fossil insects as are known is that they are very similar to those living now.[44]

Thus, first there seems to be hardly any microevolution within the insects, and secondly, their macroevolutionary origin is a complete enigma. It is very interesting that exactly this problem of the sudden appearance of higher systematic categories has also brought some paleontologists to the assumption of evolutionary "saltational mutations." The evolutionary-geneticist

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**Note added in proof.* Recent work of García-Bellido's group in Madrid (See reference 53) has supplied a fifth hypothesis on the action of homoeotic genes. By clonal analysis they have shown that growing imaginal discs are successively divided into various "compartments": first into an anterior and posterior, then into a dorsal and ventral, and a central and peripheral compartment, etc., implying that after a "compartmentalization step" cell clones are henceforth restricted to either compartment and do not overlap anymore. These researchers have adduced many arguments (e.g., the phenotypic mosaics and "transformation series" mentioned above; see Figures 8 and 9) that homoeotic genes are involved in the "compartmentalization process" and the subsequent growth program of the respective "compartments."

Sewall Wright commented on Goldschmidt's hypothesis:

> From a descriptive standpoint, it appears that this [Goldschmidt's] interpretation of the paleontological record [viz., as a succession of macromutations] has a large element of truth. *It is borne out by Simpson's quantitative studies of paleontological data* which led him to the concepts of tachytely (rapid origin of higher categories), horotely (ordinary progress) and bradytely (virtual cessation of evolution) as almost qualitatively different processes (1944).
>
> Goldschmidt and Willis[45] boldly attribute the origin of higher categories to single mutations of appropriate magnitude. Under this view the major course of evolution is simply that of the succession of the exceedingly rare viable mutations of this sort. . . . *The difficulty which most geneticists have felt with this view is that it seems to be asking for something like a miracle at each major step.*[46] (Emphasis added)

Wright preferred to view evolution as an irregularly shifting state of hereditarian, selectional, and ecological balances, and particularly as due to random genetic drift in small populations, a notion still popular in the modern "neutralist" theory. He also gave an important place to:

> . . . major mutations (homoeotic for example) which, while not adaptive at first occurrance, are not too injurious or are protected sufficiently by low penetrance, to be carried at low frequencies by the species as a part of the field of potential variability which may ultimately be used.[47]

The paleontologist who most strongly acclaimed Goldschmidt's ideas was the well-known German scientist Otto H. Schindewolf, in his book *Grundfragen der Paläontologie*.[48] On the basis of his extensive study of fossil organisms he came to the striking conclusion that the neo-Darwinian concept of random mutation and natural selection was completely inadequate as an explanation for macroevolution. He wrote (I translate):

> We are convinced that people in the evolutionary field will once come to the opinion that the thoughtless and exclusive extrapolation of the microevolutionary mechanisms to macroevolution was an error with serious consequences.[49]

He then argued that if this extrapolation were correct the realm of organisms would show the following characteristics: (a) it would appear as a continuity of forms without conspicuous gaps; (b) due to random mutation it would develop into an inarticulate, multidirectionally scattering chaos of forms; (c) it would show many overlapping and polyphyletic "circles of adaptional characters," and (d) evolution would be very slow and gradual, not periodical and saltational.

Schindewolf then showed extensively that, in fact, on all these points the contrary situation is exhibited by the fossils and encountered in nature, and concluded that, in order to account for the present organismal kingdoms as they really are, it is inevitable to assume macromutations with a complex effect. He therefore turned to genetics, namely to Goldschmidt, and wrote:

> The presentations given here have grown from an independent analysis of the paleontological material. *The more surprising and gratifying are for me the far-reaching correspondences between our* (Goldschmidt's and my) *views.* "Schindewolf's theory is practically identical with that of Goldschmidt," as D. D. Davis recently (1949) concluded on the basis of my statements from 1936. I consider these convergencies from very different starting points as a welcome indication that I am on the right road. . . .
>
> With this explanatory approach Goldschmidt has encountered various objections from other geneticists. In these disputes paleontology cannot interfere. From my own standpoint I can only add that *Goldschmidt's inferences entirely meet the requirements which the fossil material, as for me, seems to make*, and that he as the first geneticist has suggested an overall explanation which does justice to the actually historical, evolutionary data.[50] (Emphasis added).

What Homoeotic Mutants Mean to Creationists

Is it not interesting that about 1950 two bright and famous scientists, both in separate fields (the most important fields for evolutionism!), namely paleontology and genetics, independently reached the same conclusion? **Neo-Darwinism can not possibly account for macroevolution!** And they proposed the same solution: saltational mutations, as the only solution. From this realization two questions arise immediately:

(1) Have their objections to the classical synthetic theory been invalidated? Not in the slightest sense; both their paleontological and genetical arguments are still as significant as when proposed.

(2) Have their views on macromutations as essential in macroevolution then been validated? Not in the slightest sense; the views have been forgotten. Sewell Wright, who *adduced them* in 1950, did not even mention them in his extensive two volumes[51] of 1969. Lewontin did not mention them in his recent standard work[52]—he did not even mention Goldschmidt! The point is: the idea of saltational evolution has simply been even worse than neo-Darwinism.

Just look at the homoeotic mutants, and see what problems they are for macroevolutionists. I have already noted that evolution always seems to be more conceivable the less is known of the extreme complexity of certain living systems. Genetic mechanisms that explain how such systems vary do not necessarily explain how these systems originated. It is now evident that the wild-type alleles of homoeotic genes have an important role in normal genetic regulation and development. The crucial question, however, is where the homoeotic genes came from rather than how they favorably mutate.

I can imagine how genetic duplication could lead to two adjacent, identical genes which subsequently could differentially mutate. A possible example is the 47± locus in the third chromosome of *Drosophila*. But this only explains how a second, *related* homoeotic mutant could arise, not how the first homoeotic gene of that type in that chromosome region arose.

And what is worse, homoeotic genes seem very essential in controlling large batteries of either morphological genes (Waddington, Kiger) or genes in "control circuits" (Kauffman) or the "compartmentalization" of imaginal discs (García-Bellido), so that no development is at all conceivable without homoeotic genes.

Besides the problem of the very origin of homoeotic genes, the question arises how mutation of homoeotic genes could contribute to any supposed evolution. There are some very severe objections to such a conjecture, which Goldschmidt might have realized already, in part:

(a) Homoeotic organs yield two large, related disadvantages to the organism: first, no single homoeotic organ is known that is functional and therefore useful to the organism. In many cases, the homoeotic organ is even essentially destructive; e.g., all mutants of the *pb* type impede feeding and may cause an early death. Secondly, the animal is left without the original organs which were replaced by the homoeotic organs; e.g., *pod* flies cannot fly.

(b) What is needed in macroevolution is the origination of essentially new organs; but homoeotic organs are never "new" organs but always copies of organs found elsewhere in the animal. Homoeotic genes seem to "choose" between alternative developmental pathways which are all practicable in principle.

Thus, mutations of homoeotic genes would only be able to "switch on" an unusual battery of producer genes" if these genes were already available, i.e., if the organ they produce is already formed somewhere else in the body. It is absolutely inveracious and a contradiction in terms to maintain that intricate, well-ordered gene batteries could ever arise by random processes; let alone the question: through mutation of what could they arise?

(c) Homoeotic mutations are not "directional," i.e., they do not result in any appearance of higher levels of organization. In fact, I know of no mutation that could be reasonably considered to create a "higher-levelled" insect. On the contrary, most mutants should be called definite "steps back."

If evolution had taken place, a *bx pbx* individual should be called a return to the more primitive four-winged insects. Most mutants of which the names end on *-pedia* would imply a return to the evolutionary stage when all appendages were a simple parapodium, because the "legs" produced are often nothing more than rather amorphous, though clearly segmented appendages.

Now, indeed, such fall-backs could be called atavisms, and atavisms have often been considered as strong indications of evolution. But creationists have frequently pointed out that such arguments are not valid because they often lead to ridiculous inferences. Take the homoeotic examples: do the *Cbx*, the *opht*, or the *tuh* mutants imply that *Drosophila* descended (respectively) from an animal with four halteres, or with wings in the eyes, or with genital structures on the face?

Conclusions

On the basis of present knowledge of homoeotic phenomena, I come to the conclusion that they are not evidence for any evolution whatsoever. On the contrary, these phenomena are an example of how one simple gene mutation can disturb, not just one small morphological feature only, but the expression and regulation of dozens of other genes. Goldschmidt and Wright were probably correct when they stated that homoeotic mutants, because they often have a very low penetrance and expressivity, may be maintained for some time in a population. But all the facts are against the assertion that such a subthreshold state of the mutant might eventually result in a (a) functional, (b) original, as well as (c) "higher-levelled" organ. To consider this still as a possibility is just wishful thinking. In fact, nobody is doing this anymore as far as I am aware.[53]

As is the case in so many biological areas: the more data are accumulated in a certain field, the more the evidence originally used to support evolutionism shrinks away.

However, if this is so, one question always remains: although their alternative ideas have been discarded, what to do with the severe criticisms of Goldschmidt and Schindewolf regarding classical neo-Darwinism? Their refutations have definitely not been denied! Today, more geneticists than ever emphasize in contrast to neo-Darwinism that "the true nature of natural selection is most often that of an avid conservative extolling the virtue of *status quo*."[54]

Creationists have emphasized this for a long time. With great interest they follow, and sometimes participate in, the present discussion within "evolutionary genetics" as to whether microevolution (which is a misleading synonym for "genetic variation") depends largely on the natural selection of favorable mutations, or largely on the random spreading and fixation of neutral mutations. (See reference 52) But they feel more and more convinced that this discussion has no relevance whatsoever to macroevolution, i.e., the evoluiton of orders, classes, and phyla.

On this point creationists fully agree with the older evolutionists such as Goldschmidt, Schindewolf, and also Nilsson,[55] who also dared to hold the same position. Creationists feel confident that as knowledge of the impressive complexity of biological systems increases, then it will become more and more evident how naive evolutionary theorists are who consider such systems to have originated by random processes.

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