The International Journal of Comparative Psychology, Vol. 1, No. 1, Fall 1987

EVOLUTION BY PROCESS, NOT BY CONSEQUENCE: IMPLICATIONS OF THE NEW MOLECULAR GENETICS ON DEVELOPMENT AND EVOLUTION

Mae-Wan Ho

INTRODUCTION

There is much in common between comparative psychology and a biological tradition that includes such distinguished figures as poet scientist Goethe, evolutionist Lamarck, embryologist Driesch; and closer to our time, D'Arcy Thompson, Alfred North Whitehead, Joseph Needham, Richard Goldschmidt and Conrad Waddington. This tradition has been variously referred to as *organized*, *holist*, *neovitalist*, and so on, though none of the labels are completely accurate. Its chief concern is the study of living organization at different levels each with its own distinctive emphasis. Nevertheless, these people share a passionate commitment to vital process and a refusal to be seduced by simplistic pseudoexplanations at every turn.

The levels of organization apparent in the living world today have emerged in the course of evolution: from molecules and protocells (see Fox, 1984 and refs. therein) to protists; from the first multicellular organisms to communities of animals and plants, and finally to intricate human societies. All these products of evolution coexist and are interdependent *because* they are part of one evolutionary process. The key to the survival of our planet lies in a proper appreciation of the continuity which exists among the physicochemical, biological and sociocultural realms. It is from this perspective of the unity of nature that a biologist like myself may be encouraged to address psychologists on the implications that recent advances in molecular genetics have on our study of development and evolution.

This paper was written at the behest of comparative psychologist, Dr. Ethel Tobach, who was among the first to see the implications of recent findings in molecular genetics on development and evolution. I am grateful to Professor Skinner for stimulating comments, reprints and preprints and to Andrew Packard for sharing his considerable insights with me in a preprint. Thanks are also due to Peter Saunders and Brian Goodwin for helpful comments on earlier drafts.

Address reprint requests to the author: Developmental Dynamics Research Group, Open University, Walton Hall, Milton Kegnes, MK7 6AA, U.K.

Molecular Genetics Before and After the Recombinant DNA Revolution

Not so long ago, in the 1960s and early 1970s, molecular genetics epitomized a highly successful analytic approach which has dominated biology for half a century. I am referring to the developments in Mendelian and cytological genetics which led up to the discovery of DNA as the genetic material and the cracking of the genetic code. Unfortunately, this same approach, in conjunction with the neo-Darwinian synthesis, has led to the complete demise of the organism. In its place is an arbitrary ensemble of characters determined by the genes subject to natural selection over many previous generations.

This culminated in the worst excesses of sociobiology from which I hope we are finally recovering; for they are anathema to both comparative psychology and its parallel tradition in biology. Not only are we told that the biology of the human species is the product of natural selection, but that our psychology and higher mental faculties too, have all been forged by relentless competition for survival and reproduction. Many psychologists and biologists alike have recoiled from this unedifying view of human nature; so much so that they propose to sever our connections with biology altogether. Psychology and mind are in danger of being disembodied and free floating, and therefore impotent.

Actually, it is not the biology of the human species, nor indeed, biology in general which is at fault. Rather it is our perception of it through the looking glass of the Darwinian metaphor (Ho and Saunders, 1986; Ho, 1986a; Saunders, 1987). Once we begin to see biology again much as it must have appeared to people like Joseph Needham and T.C. Schneirla, we need as little fear our biology as our pyschology (or spirituality). Terms such as biological determinism, genetic determinism, or environmental determinism, for that matter, will finally disappear from our vocabulary. This is precisely what the recent advances in molecular genetics will prompt us to do, by serving as the focus for rehabilitating the organism and restoring vital process to its former richness and resplendence.

Since the advent of recombinant DNA research, molecular genetics has undergone a role reversal with regard to the concept of heredity. To appreciate this, we must realize that prior to the general acceptance of Mendelian genetics, heredity was looked upon as a process which includes development, After that, it came to mean almost exclusively the transmission of a genetic material—DNA—that remains relatively constant from generation to generation. DNA, the genotype, was believed to direct development of the phenotype, but phenotype could have no feedback influence on the DNA. Heredity was thus separated from development. Molecular genetics today, by revealing the considerable fluidity of genomic DNA and the numerous interconnections between genotype and phenotype, once again brings home to us a process view of heredity.

Heredity as Process Includes Development

The basic phenomenon of heredity is that *organisms* reproduce true to type generation after generation: acorns give rise to oak trees and eggs to chickens. The reproduction of organisms naturally includes the process of development. So much so that in 1910, T. H. Morgan considered the problem of heredity to be *identical* to that of development (see Allen, 1983). This sentiment was shared by all the leading developmental biologists and evolutionists of the time. Yet, a few years later, as a convert to Mendelian genetics mainly through his own work in chromosomal inheritance, Morgan was to insist on the separation between the *transmission* of hereditary 'information' (heredity) and the translation of this information into phenotype (development). This is a major tenet of neo-Darwinism, which, together with Weismann's doctrine, further justify the separation of evolution from development.

Weismann's doctrine is generally interpreted to mean that physiological interactions with the environment in the course of the organism's development cannot have any heritable effects because they do not lead to changes in germline DNA. (This is ironic, for Weismann himself was not really a Weismannist in that he specifically admitted physiological interactions *could* have heritable effects (see Matsuda, 1982). Weismannism itself could profit from careful reexamination.) As evolution is deemed to proceed exclusively by the selection, *a posteriori*, of preexisting genetic variants which happen to be favoured in the particular environment, the entire process of development becomes irrelevant to evolution (Maynard-Smith and Holliday, 1979). This despite the fact that developmental physiology is responsible for generating the variations acted on by natural selection.

Inherent in such an interpretation of Weismann's doctrine is the assumption that variation and selection are separate processes—as though the environment which interacts physiologically with the organism is distinct from that which selects them (see Ho and Saunders, 1982a, b). Furthermore, the generations are conceptualized as highly discrete: the experiences of each generation cannot influence the germline and so cannot be inherited.

The predominant theme of 'evolution by consequence' has pervaded philosophy, sociology (see Plotkin, 1982 and certain articles therein) and even behavioural psychology (Skinner, 1981). One does not ask where variations come from, merely what adaptive *consequence* they have. The fit between organism and environment is thus simply the result of past fortuitous variations selected by their consequences and preserved by heredity.

When we look at organisms as they are: living, breathing, acting, responding, learning, feeling, developing, and in touch with every level of

their internal and external environments at all times, it is clear that the fit between organism and environment must arise through reciprocal feedback and adjustments occurring on time scales that range from split seconds to hours and years and even generations. In other words, organisms both adapt to the environment, and adapt the environments to themselves through continuous processes nested in space and time.

Variation and Selection: One Process or Two?

Many of us have argued passionately against the idea that the genetic and environmental components of development can be neatly separated, for the weight of evidence is that the 'internal' and 'external' factors are inextricably interwoven in the physiology of development. Yet the theory of natural selection depends on just such a separation between the environment which selects and genetic variations in organisms which are selected.

In reality, we find that the presumed selective force in the environment is often precisely that which interacts with the developmental physiology of the organism to generate the variation in the first place. This is why geographic races of many species can be phenocopied by simulating the appropriate environmental conditions for development (see Ho, 1984a). Moreover, as most clearly brought home by recent findings from recombinant DNA research, the distinction between genotype and phenotype, and Weismann's barrier are both far from absolute. Organisms are interconnected wholes: psychology with biology, soma with germline, phenotype with genotype. These wholes are themselves in continuity with past and future generations, not only through biological reproduction, but also through environmental, cultural and social inheritance (see Sinha, 1984; Oyama, 1986). The intimate interrelationship between organism and environment which exists at every level makes it *necessary* to see adaptation as both immanent and simultaneous with process; and not solely as the consequence of differential survival and reproduction, such as the theory of natural selection would have us believe.

Elsewhere, I have given concrete examples to trace out the intricate multilevel and multidimensional relationships between organism and environment which continues through to genomic DNA (Ho, 1986a). Here, I shall concentrate on the processes generating form and variation: first, to demonstrate how physics and chemistry are involved; second to show how the assumption of random or fortuitous variation is untenable *because* organisms are interconnected at every level; third, to review the significant recent findings in molecular genetics and their bearing on the nature of heredity. Finally, I shall briefly outline how I see the evolution of behaviour in the process view of heredity which the new molecular genetics urges upon us.

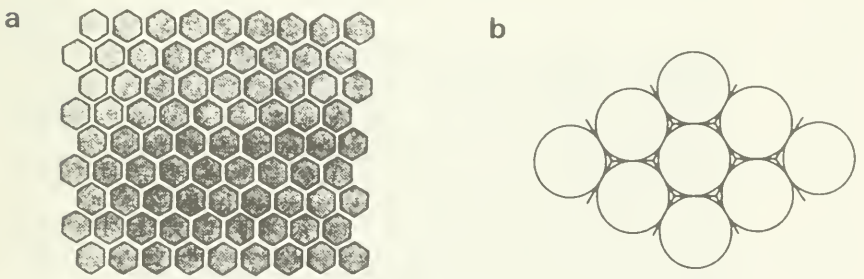
The Irrelevance of Natural Selection

In recent years, I have become very impressed with how little natural selection may actually do for evolution. More and more, I come across cases where once the mechanisms for generating form and variations are known, natural selection becomes irrelevant and even misleading as an explanation. Some examples will make this clear.

The honeycomb is a beautiful structure, each cell showing a perfect hexagonal cross-section. Darwin (1875) wrote, 'He must be a dull man who can examine the exquisite structure of a comb, so beautifully adapted to its ends, without enthusiastic admiration'. This structure Darwin attributed to the hive-making instinct of bees, perfected by natural selection. D'Arcy Thompson (1917) showed that the hexagonal cross-section of the cells, as well as their trihedral pyrimidal ends, are both the result of compression due to close packing (see Fig. 1). In other words, the impressive symmetry of the honeycomb arises from the automatic play of physical forces.

Figure 1

The structure of the honeycomb arises from uniform compression. (a) Cross-section of cells in the honeycomb, (b) a mechanical model of uniform compression giving rise to hexagonal cell (Redrawn from D'Arcy Thompson, 1917).



Mimicry—the close resemblance between different species—is often cited as one of the most convincing demonstrations of the power of natural selection. The Monarch butterfly is avoided by predators because it tastes bad. The Viceroy, on the other hand is good to eat, but is avoided by predators all the same because it resembles the Monarch. Yet this fact may explain only why the mimicry persists, not how it arose in the first place. Futhermore, as pointed out by Saunders (1984), if selective advantage were the overriding consideration, the Viceroy could simply have evolved its own bad taste instead of copying the complex wing colour pattern of

the Monarch. This strategy would have conferred an even greater increase in fitness because mimicry becomes less effective as the ratio of mimics to models increases.

The real explanation may very well be that the two species have similar patterning processes, which, in similar environments, will most likely result in convergent wing patterns (see Saunders, 1984). This developmental explanation may also account for the phenomenon of 'pseudomimicry' seen, for example, in two butterflies that are classified in different families and live on opposite sides of the globe: *Anetia cubana* in Cuba, and *Lexias aeropus* in Indonesia (Ho et al., 1986b). They are as similar as any pair of mimics, but it is difficult to see what possible advantage either of them gains from this. (Dick Vanewright, who first drew my attention to pseudomimicry, informs me that the phenomenon is by no means uncommon.)

The slime mould alternates between a multicellular slug which ends in a fruiting body bearing spores and a unicellular amoeboid phase. The amoebae feed and multiply until food runs out, then they aggregate to form a slug. Aggregation is very dramatic, involving the formation of concentric, pulsating rings. Once again, natural selection does not have anything to do with the form of these rings, which are made by a relay process. Aggregation is initiated by a pulse of cyclic AMP given off by a single amoeba, which then attracts neighbouring amoebae to move towards it and at the same time to release a similar burst of cAMP. Thus, waves of amoebae move rhythmically towards the centre of attraction, simultaneously relaying the signal outwards to other amoebae. These patterns happen to be identical to the alternating blue and orange rings created by an oscillating oxidation-reduction system known as the Belousov Zhabotinskii reaction (see Fig. 2). This remarkable similarity in form occurs in two systems which differ completely with regard to the detailed mechanisms involved. Convergence between physical and biological forms are commonplace in nature, and stems from a deep mathematical connection that transcends the details of material substrates (Thom, 1975; Saunders, 1980; see Ho, 1984b for a biologist's perspective on this issue). The next example is a further illustration.

Simple visual hallucinations such as those induced by hallucinogenic drugs have characteristic geometric forms, and originate somewhere in the brain. By using the retino-cortical projection, Cowan (1982) transforms the hallucinations into firing patterns in the visual cortex. These firing patterns turn out to be readily produced in a simple but realistic model of a network of neurons, each of which can excite both an immediate and a faroff neighbour and at the same time, inhibit the neighbour in between. The number and strength of contacts between neurons and their activation thresholds are the key parameters determining the emergence of particular patterns. The mathematics involved is similar to that describing the Belousov Zhabotinskii reaction rerferred to above, and is typical of

Figure 2

Convergence between biological and physicochemical forms. (a) Pattern of aggregation in the slime mould amoebae, (b) the Belousov Zhabotinskii reaction in a petri dish (From Winfree and Strogatz, 1983).

2a

2b

a whole class of dynamical systems which spontaneously give rise to so-called dissipative structures (see Glandsdorff and Prigogine, 1971).

In referring to all these examples of the contribution of physics and chemistry to biological forms, I do not mean to imply that explanations in terms of physical mechanism are necessarily opposed to those in terms of function. Rather, it is more the case that as D'Arcy Thompson (1917) wrote, '...like warp and woof, mechanism and teleology are woven together'. In other words, function is immanent and simultaneous with process; it does not come about as the consequence of natural selection.

Are Variations Random?

Why is natural selection deemed to be so important a mechanism of evolution? The clue lies in the assumption of randomness in the 'random variations' on which natural selection is supposed to act. Within neo-Darwinism, it has the operational meaning that nothing much could be said about the variations (see Saunders and Ho, 1984). However, many will claim it is only to be taken in the weak sense that the variations are not directly correlated with the selective force. In other words, they are supposed to arise from within the germline genome without any reference to the physiology of the organism or its external environment. In previous papers (Ho, 1986a,b), I have shown how a change in the external environment, and reciprocally, an action taken by the organism can both have deep seated influences simply because the levels of the organism are in reality fully interconnected: being conceptual 'slices' of one continuous process. Here, I want to give two examples of the nonrandom, or nonfortuitous nature of variations which reveal to us those interconnections between levels.

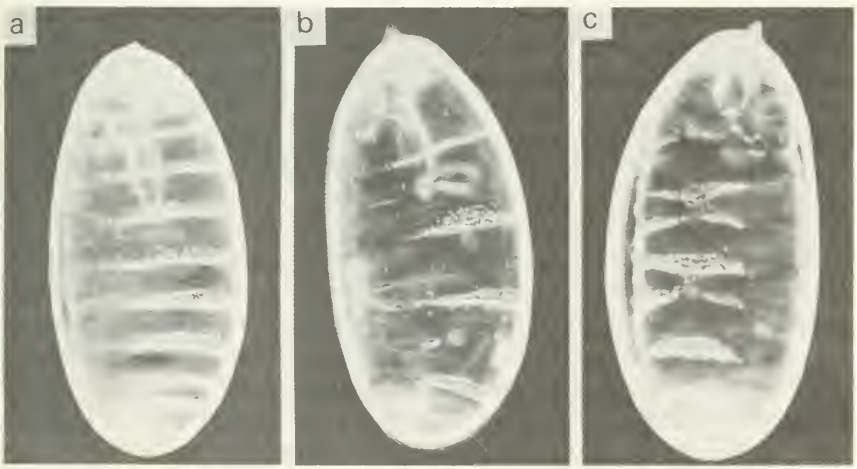
Although it is undoubtedly true that some nucleotide changes in the DNA may be fortuitous, the resulting variations in the organism are never random because they occur within the context of an epigenetic system which is highly structured. This dynamical structure in turn gives *shape* to the variations. So it is that the same variations can come either from mutations or from the appropriate environmental perturbations. While I do not claim that it is possible to generate so-called phenocopies of every mutation (though it may be true), it is certainly the case that if we know the timing of particular developmental events and can make a shrewd guess at the mechanism involved, then we can induce the phenocopies we have in mind.

A number of morphogenetic mutants of the fruitfly have been isolated and molecularly cloned recently (see Coulter and Wieschaus, 1986, and references therein). These cloned genes are being used most ingeniously to locate the temporal and spatial domains of their expression during embryogenesis. The fruitfly's body is made up of about 14 repeated parts or segments, each of which has a different identity. Mutations in the so-called

homeotic genes scramble the identity of segments, whilst mutations in the *segmentation* genes mess up the way the body is divided up into segments. The phenomenology of embryogenesis has been greatly enriched by molecular genetics, but these studies simply do not address the problem of how the genes become expressed in their particular spatial configurations during development. Spatial organization is inititated by physicochemical processes in the cytoplasm; these set up the spatial patterns of cellular cytoplasmic states that in turn trigger the differential expression of genes (see Ho, 1984a). Thus, a simple physical perturbation—exposure to ether) is sufficient to induce a range of segmentation defects in *Drosophila* (see Ho et al., 1986a). Specific defects are repeatably induced at precise stages of development. Many of these resemble mutant phenotypes which have been described, and so may be regarded as phenocopies. Figure 3b depicts a phenocopy of the so-called pair-rule mutant, *even-skipped*, which has only half the number of body segments. A substantial number of the phenotypes obtained are new, and have never been described as mutants. One of these, which I call 'bows', is given in Figure 3c. It will be of interest to see if a 'genocopy' of this will eventually be produced by mutation.

Figure 3

Expression of unusual phenotypes in embryos of *D. melanogaster* as the result of environmental perturbation. (a) Normal embryo, (b), (c), embryos treated with ether (see text).



Wild type *E. coli* metabolizes lactose by first breaking it down with the enzyme β-galactosidase. Mutant strains in which the β-galactosidase gene is deleted have no enzyme activity and do not metabolize lactose in minimal medium with other carbon sources present. Experimenting with these mutant strains, Campbell et al., (1973) found that when the other carbon sources were exhausted, mutant colonies appeared which pos-

sessed lactose-splitting activity. The enzyme responsible was not the B-galactosidase that had been deleted, but another enzyme altogether, called *ebg,* mapping to the opposite side of the genome. This had undergone mutations which gave it lactose metabolizing activity. By itself, this result is unremarkable because it could be interpreted as the artificial selection of a fortuitous variation. However, the experiment was immediately repeated by other workers (Hall and Hartl, 1974), who isolated 34 different lactose-utilizing strains by the same method. All of these contain enzyme activity *identical to ebg.* Moreover, in 31 of the strains, the synthesis of the newly evolved enzyme is regulated by lactose; ie, there must have been a mutation in another gene which interacts with lactose to regulate ebg. There is nothing fortuitous about this highly repeatable response to the same environmental challenge, which involves in all likelihood the same mutation(s) in two different genes appearing simultaneously (see Opadia-Kadima, 1987). But this example is no different from the repeatable production of specific phenotypes when a given environmental perturbation is applied at a particular developmental stage in *Drosophila* embryos. It is the physiological state of the cell in one case, and the epigenetic system of the organism in the other, that organically 'selects' the appropriate response. Part of that response may involve defined mutations at specific sites in the genome.

Today, we have many more examples of directed, nonrandom changes in the genome (see below). The striking feature in the *E. coli's* acquisition of novel function is that it is so obviously adaptive as well as nonrandom. A comparable situation in higher organisms which comes to mind is the specific and reproducible nature of the immune response to particular antigens. A great deal of antibody diversity is generated by DNA rearrangements which splice different combinations of three to four genes together to make a different composite antibody gene in each lymphocyte. In addition, somatic mutations in the antigen-binding site improve binding affinities during the maturation of the immune response. Analysis of the antibodies produced against a given antigen reveals that the same mutations recur, not only among different antibodies in the same mouse, but among antibodies produced in different mice as well (Griffiths et al., 1984).

What impresses us in the above examples, is that there is one *continuous* process of the organism responding physiologically to the environment. The environment is 'selective' in so far as it selects, via the physiological system for an appropriate response, but no real 'selective deaths' have taken place as required by natural selection. The fact that the response sometimes involve genomic changes shows that the strict dichotomy between genotype and phenotype really does not exist as far as the organism is concerned.

As the variation is first generated by physiological interaction between organism and environment, the persistence of that variation over the generation depends, not on natural selection, but on hereditying! The

variation would indeed persist in the absence of natural selection, so long as heredity operates in its favour. There is a great deal of conceptual confusion here which some good philosopher of biology should try to sort out. Meanwhile, I shall go on to consider the nature of heredity itself.

Heredity Before and Since the Recombinant DNA Revolution

Until very recently, heredity was supposed to be due to the transmission of something which remains basically unchanged from generation to generation. The widespread use of the term 'inheritance' is significant, as it brings to mind something akin to the family heirlooms. This concept depended on the constancy of DNA both during development and in reproduction (see Ho, 1986a).

Let us review the basic assumptions of genetics in the 1960s and early 1970s (which are to be found in any textbook on genetics):

1. DNA (and in some viruses, RNA) is the genetic material.
2. Genetic information flows from DNA to RNA to protein, but never in reverse.
3. One polypeptide is specified by one gene locus.
4. Collinearity exists between the base sequence of DNA in the gene and the amino acid sequence of the polypeptide it encodes.
5. The genetic code is universal.
6. The codons are read in one direction, without overlap, and only in one correct reading frame.
7. With very few exceptions, the DNA of all cells remain constant during development, only the genes expressed differ between different cells.
8. Environmentally induced modifications do not affect the DNA and cannot be inherited.

Since then, all but the first assumption have become violated. (The first assumption remains true only by virtue of definition, as it has been long accepted that certain cytoplasmic components of the oocyte also affect heredity, and therefore would qualify as 'hereditary material', if not 'genetic material'.) Some of the violations preceded the main recombinant DNA revolution (see Ho 1986a,b; Ho and Goodwin, 1987). In my view, the watershed is the discovery of interrupted genes, which shows that the sequence of bases in the gene is not collinear with the sequence of amino acids in the polypeptide (see Chambon, 1981). Instead, the coding sequence is interrupted at intervals by long stretches of noncoding sequences, which are spliced out during *processing* of the primary transcript. Most vertebrate genes examined are interrupted, as well as some genes of eukaryotic microorganisms such as the yeast.

By far, the most significant picture to emerge out of recombinant DNA research is the dynamism and flexibility of the eukaryotic genome in both

its organization and function. This is in striking contrast to the relatively static and mechanical conception which previously held sway.

Flexibility in Gene Function

Some idea of the functional flexibility may be gleaned by reexamining the status of the one gene-one polypeptide relationship which was fundamental to genetics prior to recombinant DNA research. This relationship has since been violated so many times, and in so many ways that there appears no longer to be any general rule in the matter (Ho, 1987b). It really exposes the fallacy of the idea that single genes could be involved in 'determining' any single character. This assumption underpins the whole theoretical edifice of sociobiology; despite elaborate apologies to the contrary (see Saunders, 1987).

For example, the mechanisms which process the primary transcript into messenger RNA inherently allow for much flexibility as to which bits of the coding sequences are joined together. Sure enough, alternative processing does occur for the primary transcript of some genes to give more than one species of mRNA, which are subsequently translated into different polypeptides (see Watson et al., 1983). Alternative processing occurs as part of normal development to give different proteins in different tissues, or in the same tissues at different times.

Other mechanisms of gene expression involve rearrangements of the DNA itself prior to transcription, so that many genes may be brought together to make a polypeptide. This mechanism was first discovered for the immunoglobulin light and heavy chains (see Hood et al., 1984), and has since been demonstrated also in the T-lymphocyte cell surface receptor proteins which recognize foreign antigens (see Robertson, 1984, and references therein).

The idea of the gene as a simple, well-defined locus in the genome does not now apply to over half of all the genes that have been molecularly cloned. Each of these genes actually exists as families of repeated sequences, or *multigene families* (see Watson et al., 1983). Multigene families may be arranged in one or more clusters of tandem repeats. Some have nearly identical sequences, and function simultaneously to expand the amount of the same protein synthesized. In other cases, the gene of families, though clustered, are not identical, but code for related proteins.

Apart from the multigene families with identifiable and functional gene products, there are also families of repeated sequences with unknown function which are highly dispersed throughout the genome. The number of copies vary for each sequence from less than ten to many thousands or hundreds of thousands. These dispersed repeats are ubiquitous in genomes of all higher organisms, in some cases making up 70% of the genomic DNA present (see Dover and Flavell, 1982). Many of these can change places, expand and contract in number, or even convert one

another's sequences within the family. These structural alterations are often intimately involved with gene function (see below).

In short, every conceivable relationship between genes and polypeptides has been found to exist: one-one, one-many, many-one, and many-many. The functional flexibility of the genome is in part associated with, and indeed, fully matched by its structural fluidity. This in turn locates the genome firmly within the physiological system of the organism as a whole, as we shall see.

I will now concentrate on the two main aspects of the recent findings in molecular genetics which are most relevant to my thesis of evolution by process.

The Fluid Genome

The first is the fluidity of the genome, which refers to all observations suggesting that genomic DNA is subject to relatively large alterations both during development and in evolutionary time. Genomic fluidity depends on a host of mechanisms which can rearrange DNA (such as that involved in the synthesis of imunoglobulins), move or transpose sequences around the genome, mutate sequences, greatly amplify particular sequences or same or different part of the genome (see Ho, 1986a,b; and references therein).

It is not known whether entire genomes are potentially fluid, though a great deal of actual fluidity is associated with the multigene families witl dispersed sequences. Some parts of the genome are known to change in a predictable way during development. Others have been found to change in both predictable and unpredictable ways under different kinds of environmental conditions. For example, mammalian somatic cells, both *in vivo* and *in vitro* undergo nonrandom multigenic amplifications when challenged with cytotoxic drugs. These changes involve reproducible molecular as well as gross chromosomal aberrations (Gudkov and Kopnin, 1985).

More dramatically, large changes in germline DNA can be induced by environmental manipulations within a single generation. The best studied example is the induction of heritable changes in flax plants treated with different fertilizers (see Cullis, 1983). The stable lines produced differ from the parental lines and from one another in morphological characters, isoenzyme patterns, as well as in amounts of nuclear DNA, the number of ribosomal RNA genes and other repeated sequences.

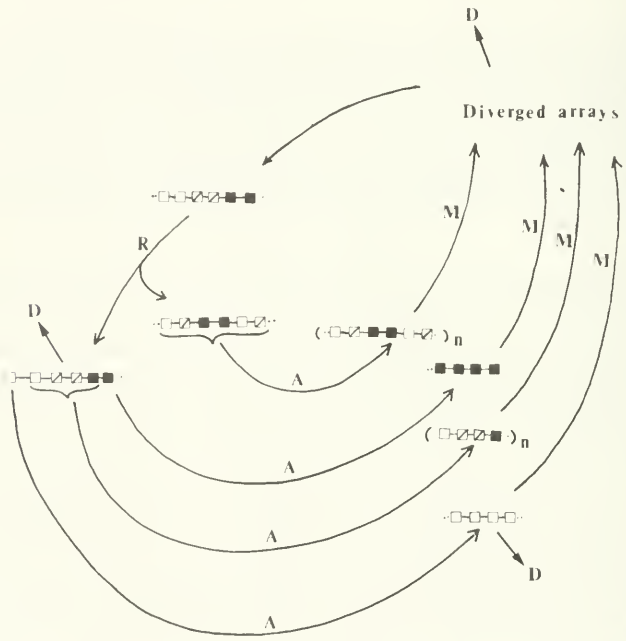
A substantial amount of genomic fluidity with essentially unpredictable outcomes results from the transposition of mobile genetic elements. Transpositions have been shown to be particularly frequent during stress in both maize and Drosophila (see McClintock, 1984; Temin and Engels, 1984). They mutate other genes by inserting into or near them so that the latter become either activated or inactivated. Transpositions also cause gross chromosomal rearrangements, thus scrambling the genome in a

major way. Transpositions occur not only in somatic cells but also in germ cells so that the resulting mutations and scrambled genomes are passed straight on to the next generation.

A comparison of multigene families from related species suggests a relatively high background rate of DNA 'turnover' in all organisms due to cycles of rearrangements, amplifications, deletions and mutations (Fig. 4). This leads to species divergence in the long term. In addition, some people

Figure 4

Dynamics of genomic 'DNA turnover'. A, amplification; D, deletion; R, rearrangement; M, mutation. Different square symbols represent different gene sequences (Redrawn from Flavell, 1982).



suggest that under certain environmental conditions, the same mechanisms responsible for DNA turnover can give sufficiently large genetic changes to precipitate the rapid formation of new species (see Cullis, 1987; Pollard, 1987). Both kinds of speciation occur independently of natural selection.

In summary, DNA may be just as responsive and flexible as the rest of the organism, from behaviour to developmental physiology to protein synthesis (see Ho, 1986a). In fact, genomic fluidity can itself be regarded as a phenotypic character which varies between lines, between species, and

according to the environment and the physiological state of the organism (Cullis, 1987).

The Permeability of Weismann's Barrier

The second aspect of the findings from recombinant DNA research is the permeability of Weismann's barrier (see Pollard, 1984; Ho, 1986a). This involves all sorts of processes in which the soma talks back to the germline as part of the functional interaction between different levels within the organism or between the organism and the external environment. I would include:

a. The large scale reverse transcription of processed RNAs into DNA and reinsertion into the germline genome.
b. The nonrandom changes in genomic DNA in certain environments which become stably inherited in subsequent generations.
c. Biased gene conversion with or without mRNA intermediate, which depends on functional feedback to genomic DNA.

Note that I have not included the other non-Mendelian processes mentioned above in connection with genomic fluidity, nor the now well-established horizontal transfer of genes between individuals and between species by viruses and plasmid vectors, because they do not seem to be *directly* related to physiological functions. (It should be noted that in the transfer of plasmids carrying antibiotic resistance genes among micro-organisms, there is an indirect involvement with physiological functions.) But that only reflects the extent of my ignorance at this juncture. It may be that as further knowledge becomes available, these other non-Mendelian processes will prove to be part and parcel of the organism's repertoire in the performance of its vital functions.

Reverse transcription plays a large role in shaping the eukaryotic genome (Baltimore, 1985). Since its discovery in retroviruses associated with cancer, the same process has been identified in a wide variety of organisms. For example, certain eukaryotic transposable elements are very similar to retroviruses, and transpose by reverse transcription of processed RNA. Vertebrates cells have cytoplasmic particles which are similar to retroposons (mobile genetic elements which transpose via RNA intermediates). These have active reverse transcriptase and are represented in the genome as proviral DNA, accounting for some 0.3% of the chromosomal DNA of the cell. That reverse transcription occurs frequently for eukaryotic genes is strongly suggested by the widespread presence of so-called *processed pseudogenes* in the genome both for single copy gene sequences and for multigene families. These are reverse transcribed from mRNA into DNA and reinserted into the genome. One particular sequence, the *Alu*, repeated half a million times in the human genome, is reverse

transcribed from the cytoplasmic RNA of the 'signal recognition particle' involved in translocating protein into and across cytoplasmic membranes. Most pseudogenes are probably nonfunctional; but one of the rat insulin genes has been shown to be a functional retroposon (Soares et al., 1985).

More intriguing still is the recent report that a certain family of repeated DNA sequences in primates, the L1, may be derived from a sequence encoding a reverse transcriptase-like protein (Hattori et al., 1986). It will be of interest to see whether the protein does have reverse transcriptase activity, and if so, whether reverse transcription is part of the normal functional repertoire of the organism.

Reverse transcription violates the central dogma as well as Weismann's barrier. Some people argue that the violation of the central dogma may be confined within germ cells, and so for the organisms in which germline and soma are well separated, this does not constitute a violation of Weismann's barrier. As pointed out by Buss (1983), however, there is no early separation between germline and soma in protists, fungi, plants, and over half the existing phyla of animals. In addition, the presence of processed pseudogenes in proteins such as the haemoglobins, which are expressed only in specialized somatic cells, suggests that communication from somatic to germ cells can occur, possibly by way of retroviral infection (Temin, 1971; see also Pollard, 1984). Indeed, cellular mRNAs are often found associated with isolated retroviral particles. Ikawa et al. (1974) showed that when Friend leukemia virus was grown on red blood cells that were actively transcribing globin genes, one in a thousand of the virus particles had managed to package β-globin mRNA inside.

I have already mentioned the directed changes in genomic DNA on treating flax plants with different fertilizers. These changes are specific to different environments and reproducible for each environment; so they are not generalized stress responses. The genomic changes occur in the course of development, and involve all cells in the meristem simultaneously. Subsequent to that, the plants improve in growth. Thus, at least some of the changes may constitute an adaptive physiological response which is thereafter stably inherited (see Cullis, 1987).

Biased gene conversion is a tantalizing mystery at the moment. It involves the transfer of sequences between homologous genes present in different parts of the genome. Biased gene conversion contributes to so-called 'concerted evolution' in which members of a multigene family become more homogeneous within a given species than between species (see Dover, 1986 and references therein).

Apart from its obvious contribution to genomic fluidity, gene conversion may be related to gene function especially if an RNA intermediate is involved. In that situation, expressed genes (which are transcribed and processed into mRNA) will convert nonexpressed homologous sequences. Also, if there is some correlation between the state of methylation of a gene and its expression, then methylated genes which are not expressed may

become preferential targets for conversion (see Kourilsky, 1986; Doolittle, 1985). This would constitute yet another example of a physiological adaptation that involves genomic DNA changes, but in such a way as to stabilize and maintain those gene sequences that are expressed. That gene sequences may be dynamically stabilized by function is also suggested by the recent report that expressed genes are repaired four times as efficiently as inactive genes after exposure to ultraviolet radiation (Madhani, et al., 1986).

In conclusion, genomic DNA is not immune to change as the result of feedback from the environment and from higher level physiological states within the organism. In fact, DNA changes are involved in the stabilization of gene function as much as in altering it. This only reflects the necessary relationship which DNA has with the rest of the organism. In a sense, there is nothing special in the status of DNA. Elsewhere (Ho, 1986a,b) I have shown that gene expression states can be stably inherited without changes in DNA. Here, we have examples of alterations in DNA instigated by changes in the environment within one generation, which can become inherited.

The Need to Reformulate Heredity

The real problem of heredity is to account for the stable and repeatable nature of reproduction. This feature was previously widely attributed to the constancy of DNA. The major consequence of the discovery of the fluid genome is to expose the untenability of this assumption. DNA is functionally and structurally as flexible as the rest of the organism. How then should we see heredity? Where does stability reside if not in the constancy of DNA? In order to answer this question, we have to remind ourselves of some elementary facts of biology.

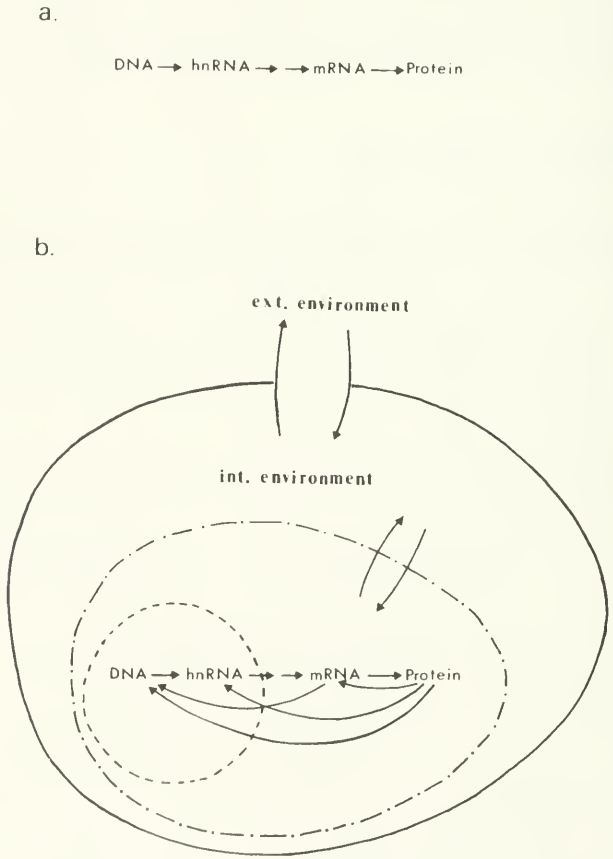
Living beings engage in the process of living. Process is an *activity* at all levels: from the behaviour of organisms in their ecological and social environment to the expression of genes in their cells. From the beginning of development to maturation and senescence, there is almost nothing that remains static and unchanging. Molecules turnover in metabolism and growth. Cells and tissues undergo morphogenesis and differentiation, die and are replaced as the organisms develop. Organisms are life histories and not mechanical objects (as conceptualized within neo-Darwinism (see Ho, 1986a)). Whereas the stability of mechanical objects depends on static equilibrium, that of organisms is *dynamically maintained*, and is utterly dependent on activity; in other words, on fluidity and change. The cessation of activity spells death.

Heredity—a name given to the observed constancy of reproduction—must ultimately be looked upon as process, and not as some *material* which is passed on from parent to offspring. Processes, whether biological or physicochemical, have an inherent dynamic which generates pat-

terns and regularities (recall the aggregation of the slime mould, the visual hallucinations and the Belousov Zhabotinskii reaction mentioned earlier); and here is where the stability of reproduction resides. Another important aspect of heredity, closely connected with the dynamic stability we have been describing, is that the 'control' of development is web-like and *circular*, rather than linear and unidirectional (see Fig. 5). This means that *the 'cause' of development is not just the DNA, but is instead distributed throughout the complex interrelationships between the different levels of*

Figure 5

Two models of gene function in development. (a) The central dogma. (b) The process view (this paper). hnRNA, heterogeneous nuclear RNA or primary transcript.



organism and its environment. The fluidity of DNA, far from being paradoxical, plays an important and indispensible role in the maintenance of

the organismic system as a whole. The components of the system must be able to adjust and respond as appropriate to their particular *milieu*. Thus, we have seen how gene function can lead to changes in DNA which reinforce that function. What is inherited in each successive generation is not only the precise copies of DNA molecules in the parents, but an entire experiential repertoire including maternal, cyctoplasmic effects, the physicochemical, biotic and social environments (Ho, 1986a,b), all of which conspire to make development similar to the previous generation. Heredity is therefore inseparable from development.

Similarly, development is directly linked to evolution in two senses. The first is in the formal sense that development, through the dynamical structure of the epigenetic system, defines the sort of changes that can occur under different contingent conditions. The second is by virtue of the fact that the generations are not discrete and the germline not so inviolable as previously thought. The strict impermeability of Weismann's barrier is an idealization which has little physiological basis. This means that the experience of each generation will quite likely have a physiological as well as sociocultural influence on subsequent generations.

In a way, it is as misleading to distinguish 'physiological' from other influences as it is to categorize 'internal' as opposed to 'external' factors, even though it may often be convenient to do so. The reason is that external factors are internalized, just as internal factors become externalized in the course of development. It is because of this intimate interramification that adaptive evolution can occur. To impute this fit between organism and environment to the consequence of natural selection is simply to reduce and mystify vital process out of existence. After all, nobody would seriously think we need natural selection to account for the complicated shapes of snowflakes, or the concentric rings of the Belousov-Zhabotinskii reaction. These forms are the automatic outcome of the prevailing 'environmental' parameters acting in concert with the physical properties of water in one case, and the chemical properties of the reactants in the other.

I do not claim that living organisms are just like physical systems. They are not. Organisms exhibit heredity. It is that which requires explication in terms of the dynamics of interrelationships between organism and environment. Similarly, the key to evolution lies not in natural selection, but in the nature of changes which can occur in those systems in the course of generations; in their resilience to certain perturbations and susceptibilities to others. This is where we ought to be devoting our time and energy, rather than in thinking of selective advantage of atomistic traits.

The Process View of Evolution

How does one see evolution by process as opposed to evolution by consequence? This is really the subject of at least another paper, but I will

outline an approach towards which a number of workers in the field of animal behaviour are already evolving, although they themselves may not necessarily see it as so.

One of the first concerns (Packard, 1986) is to restore the notion of 'fitness' to its former meaning (cf. Henderson, 1917) as an appropriate or harmonious relationship between organism and environment, rather than as a measure of reproductive success. Such fitness arises simultaneously with the organism acting and responding to the environment in continuous processes occurring at multiple levels over a range of time scales. It does not result from random variations which are selected *a posteriori*. The experiencing organism registers change as it is experiencing, and this will influence its future actions and experiences as well as those of the next generation. This is where I believe Skinner's analogy between the consequence of reinforcement and the consequence of selective reproduction must break down. The consequence of reinforcement involves the registering of real experience by the organism; as Skinner had said somewhere, an experienced rat is a 'changed rat' (Skinner, 1984). On the contrary, no such registering of real experience is permitted in the neo-Darwinian theory of natural selection. In fact, this is specifically forbidden on account of Weismann's barrier. If one accepts the arguments presented in this paper, then there is a *continuity*, and not just an analogy between operant reinforcement within one generation and reinforcement by the process of heredity in successive generations. This is a worthwhile project for future exploration.

Another issue I cannot deal with in detail is the notion of active choice (see Ho, 1984b) which a number of neo-Darwinist ethologists and biologists have emphasized. However, the role of choice is at best ambiguous within neo-Darwinism. While the animal is invested with the capacity to choose, it is the *consequence* of the choice which is supposed to be selected and inherited, thus making the act of choosing meaningless. This contradiction arises most obviously in the juxtaposition of mate *choice* and sexual *selection* as the consequence of the choice made (see also Bateson, 1987).

If choice is to be really exercised, then it is the ability to choose that is inherited, and not the choice itself. Of course, the extent to which choice is 'free' is another matter. Animals are social beings which seek approval, if not love; and experience both pleasure and pain. It has been suggested that such psychological states may play a large role in the evolution of behaviour in influencing the animal's choice (Packard, 1986). This means that the animal itself is evaluating at all times, both its own actions (by a 'sense of satisfaction' (Skinner, 1985) perhaps in relation to its social *milieu*), and the effect of its actions on the environment. It is not 'judged' a *posteriori* by natural selection.

In order to make this discussion more concrete, let us consider predation. The Darwinian picture is that the prey evolves because the weakest,

slowest running prey, and their bad genes, get eliminated by the predator. By the same token, the fastest, most cunning predators capture the prey and leave the most offspring, thus preferentially propagating their good genes. The only thing which prevents both predator and prey from evolving towards the speed of light is some vague and timely appeal to 'developmental constraints'.

A more rational view of the whole process may be as follows. The prey, having survived the predator, and reciprocally, the predator, having successfully (or for that matter, unsuccessfully) preyed, both register the experience. The imprints of the experience go from the visual/olfatory systems to ionic currents and physical, biochemical membrane changes in the central nervous system in the short term (Farley et al., 1983; Mason and Rose, 1986). These translate into changes in neural synapses and synthesis of glycoproteins and perhaps neuroreceptor molecules in the longer term (see Rose, 1986). Similarly, the exercise of muscles involved in running either to catch the prey or to escape from the predator, will effect alterations in the contractile properties of the muscles (Lamb et al., 1974), which include the type of nerve endings present, and the expression of different ATPases and myosin genes (see Laing and Lamb, 1985, and references therein).

These imprints, which are really internalizations of the environment at successive levels in space and time, may then alter heredity in the sense reformulated here and elsewhere (Ho, 1986a,b). At the 'highest' level, cultural inheritance will ensure that the next generation of both prey and predator will be taught to deal effectively with each other. Social cohesion will encourage a conformity of behaviour among individuals all of whom will reinforce later generations. At the 'lowest' level, the change in gene expression states may be inherited cytoplasmically, or maternally. It is not impossible, though not necessary, that changes in genomic DNA may also be involved. This is open to investigation by techniques now available.

Skinner's hypothesis that operant conditioning and reinforcement are involved in shaping and maintaining behaviour does have the virtue that the entire process can be made quite transparent. One starts from the external environmental stimuli, and ends perhaps in changes at the molecular genetic level. There is no need of 'genetic programmes' or of unknown and unknowable 'internal representation states' to 'control' behaviour. By the same token, there is no need to appeal to 'genes for reinforcement' as Skinner (1981) has done; especially if all organisms are supposed to have them, for genes are primitively defined on *differences*.

The process view of evolution that I have presented is at one with the dynamic holism that Schneirla (1966) and others have advocated: a description that loses nothing of the texture and colour of reality. It is necessarily pluralistic because it involves all levels and their interconnections (cf. Tobach and Greenberg, 1984). All nature is continuous from the inorganic to the biological and cultural domains.

The continuity of nature does not legitimise the rampant reduction of all phenomena to the 'lowest level' of the molecules. The ultimate failure to locate heredity exclusively in DNA should serve as a lesson for us all. On the other hand, continuity does not entail a nebulous holism in which everything is connected to everything else. It is for us to work out what precisely the connections are.

By far the strongest objection to reductionism is that there is no direct one-to-one translation between levels. Thus, a genetic mutation *per se* is not sufficient explanation for organismic change. It is the mutation in the context of the developmental or epigenetic system which must be considered.

Just as organisms cannot be reduced to a sum of genes, societies cannot be reduced to a sum of individuals. This applies to both human and animal societies. Deborah Gordon (1986) shows that ant colonies exhibit repeatable patterns of group behaviour which are supervenient over the behaviour of individuals. Thus, there are level-specific regularities that should be investigated in their own right, and more importantly, these regularities constitute parameters which can determine the behaviour of the constituent parts. I have traced the line of determinative influence from sociocultural environment to individual behaviour, physiology and 'down' to the genes in previous papers (Ho, 1986a,b).

It seems clear that the directions of causation are both 'upwards' from the genes to the environment and the reverse. But even this is an oversimplification. First of all, it leaves out the organism as an active agent whose conscious action will have effects not only in its internal physiology but also on the external environment. These effects will either reinforce each other towards the repetition of the act; or they may lead to rapid change through runaway positive feedback loops (see Ho, 1986a) or cascades (Gray, 1987). Secondly, the concept of levels itself needs reexamining. I do not believe that levels are ordered so neatly for our benefit: there is really one continuous process nested in space and time. Although the living world appears to have evolved in a hierarchical manner, the existing relationships between levels may be strongly heterarchic. This would not be surprising in view of the fluid and often prompt responses of DNA and proteins to various 'higher' level stimuli. It is definitely an area which merits future investigation.

Molecular genetics today signals the ultimate collapse of the mechanical, atomistic paradigm it epitomised, which has dominated biological sciences since the rise of neo-Darwinism (see Ho, 1986a). In this respect, molecular genetics has become its own antithesis. While its techniques are among the most powerful that modern science has to offer, its findings are compelling us to reexamine the very conceptual basis of heredity itself. The result is a dynamic, holistic view of nature which is consonant with real experience.

I would like to end by locating the human species firmly within nature; not a nature red in tooth and claw, but one of process and creativity where biology is connected with, but by no mean dominant over, culture and mind. In reasserting our unity with nature, we are thereby enpowered to construct our own destiny.

REFERENCES

Allen, G. E. & Morgan, T. H. (1983). The influence of mechanistic materialism on the development of the gene concept 1910-1940. *Amer. Zool.*, *23*, 829-843.

Baltimore, D. (1985). Retroviruses and retrotransposons: the role of reverse transcription in shaping the eukaryotic genome. *Cell*, 481-482.

Bateson, P. (1987). The active role of behaviour in evolution. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metaphors.* London: Wiley.

Buss, L. W. (1983). Evolution, development and the units of selection. *Proc. Nat. Acad. Sci.* (USA), *80*, 1387-1391.

Campbell, J. H. Lengyel, J. A. and Langridge, J. (1973). Evolution of a second gene for B-galactosidase in *E. coli. Proc. Nat. Acad. Sci.* (USA), *70*, 1841-1845.

Chambon, P. (1981). Split genes. *Scient. Am.*, *224*, 60-71.

Coulter, D. & Wieschaus, E. (1986). Segmentation genes and the distributions of transcripts. *Nature*, *321*, 472-474.

Cowan, J. D. (1982). Spontaneous symmetry breaking in large scale nervous activity. *Int. J. Quant. Chem.*, *22*, 1059-1082.

Cullis, C. A. (1983). Environmentally induced DNA changes in plants. *CRC Critical Reviews in Plant Science*, *1*, 117-131.

Cullis, C. A. (1987). Control of variation in higher plants. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metaphors.* London: Wiley.

Darwin, C. (1875). *Origin of species* (6th ed.), London: John Murray.

Dover, G. A. (1986). Molecular drive in multigene families: how biological novelties arise, spread and are assimilated. *TIG*, *2*, 159-164.

Dover, G. A. and Flavell, R. B. *Genome evolution*, London: Academic Press.

Doolittle, W. F. (1985). RNA-mediated gene conversion? *TIG*, *1*, 64-65.

Farley, J., Richards, W. G., Ling, L. J., Liman, & Alkon, D. L. (1983). Membrane changes in a single photoreceptor cause associative learning in hermissender. *Science*, *221*, 1201-1203.

Flavell, R. B. (1982). Major sources of variation during species divergence. In G. A. Dover & R. B. Flavell (Eds.), *Genome Evolution.* London: Academic Press.

Fox, S. W. (1984). Proteinoid experiments and evolutionary theory. In M. W. Ho & P. T. Saunders (Eds.), *Beyond neo-Darwinism: introduction to the new evolutionary paradigm.* London: Academic Press.

Glansdorff, P. & Prigogine, I. (1971). *Thermodynamic theory of structure, stability and fluctuations*, London: Wiley.

Gordon, D. (1986). The dynamics of group behavior In P.P.G. Bateson & P. H. Klopfer (Eds.), *Perspectives in ethology.* New York: Plenum Press.

Gray, R. (1987) Metaphors and methods in evolutionary theory. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metophors.* London: Wiley.

Griffiths, G. M., Berek, C., Kaartinen, M. & Milstein, C. (1984). Somatic mutation and the maturation of immune response to 2-phenyl oxazolone. *Nature*, *312*, 217-275.

Gudkov, A. & Kopnin, B. (1985). Gene amplification in multidrug-resistant cells: molecular and karyotypic events. *BioEssays*, *3*, 68-71.

Hall, B. G. and Hartl, D. L. (1974). Regulation of newly evolved enzymes 1. Selection of a novel lactase regulated by lactose in *Escherichia coli. Genetics*, *76*, 391-400.

Hattori, M., Kuhara, S., Takenaka, O. & Sakaki, Y. (1986). L1 family of repetitive DNA sequences in primates may be derived from a sequence encoding a reverse-transcriptase-related protein. *Nature*, *321*, 625-628.

Henderson, L. H. (1913). *The fitness of the environment*, New York: MacMillan.
Ho, M. W. (1984a). Environment and heredity in development and evolution. In M. W, Ho & P. T. Saunders (Eds.), *Beyond neo-Darwinism: An introduction to the new evolutionary paradigm.* London: Wiley.
Ho, M. W. (1984b). Where does biological form come from? *Rivista di Biologia, 77*, 147-179.
Ho, M. W. (1986a). Genetic fitness and natural selection: myth or metaphor. In E. Tobach & G. Greenberg (Eds.), *Proc. 3rd T.C. Schneirla conference on behaviour and evolution.* New Jersey: Lawrence Erlbaum Assoc.
Ho, M. W. (1986b). Towards a radical reformulation of heredity. *Rivista di Biologia, 79*, (in press).
Ho, M. W. (1987). *Genes and generation, Unit 8, An open university course*, Milton Keynes: Open University Press.
Ho, M. W. (1987b). On not holding nature still. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metaphors.* London: Wiley
Ho, M. W. & Goodwin, B. C. (1987). *Genes and generation, Unit 1, An open university course*, Milton Keynes: Open University Press.
Ho, M. W. & Saunders, P. T. (1979). Beyond neo-Darwinism: an epigenetic approach to evolution. *J. theor. Biol., 78*, 573-591.
Ho, M. W. & Saunders, P. T. (1982a). Adaptation and natural selection: mechanism and teleology. In S. Rose (Ed.), *Towards a liberatory biology.* London: Allison and Busby.
Ho, M. W. & Saunders, P. T. (1982b). The epigenetic approach to the evolution of organisms—with notes on its relevance to social and cultural evolution. In H. C. Plotkin, (Ed.), *Learning, development and culture.* London: Wiley.
Ho, M. W. & Saunders, P. T. (1986). Evolution: natural selection or self-organization? In C. W. Kilmister, (Ed.), *Disequilibruim and self-organization.* Dordrecht: D. Reidel.
Ho, M. W. & Matheson, A., Saunders, P. T., Goodwin, B. C. & Smallcombe, A. (1986a). Ether-induced segmentation defects in *Drosophila melanogaster.* (submitted).
Ho, M. W., Saunders, P. T. & Fox, S. W. (1986b). A new paradigm for evolution. *New Scientist*, 41-43.
Hood, L. E., Weissman, I. L., Wood, W. B. & Wilson, J. H. (1984). *Immunology* (2nd Ed.), Menlo Park: Benjamin.
Ikawa, Y., Ross, J. and Leder, P. (1974). An assoication between globin messenger RNA and 60s RNA derived from friend leukemia virus. *Proc. Nat. Acad. Sci.* (USA) *71*, 1154-1158.
Kourilsky, P. (1986). Molecular mechanism for gene conversion in higher cells. *TIG, 2*, 60-63.
Laing, N. G. and Lamb, A. H. (1985). Muscle fibre types and innervation of the chick embryo limb following cervical spinal cord removal. *J. Embryol. exp. Morph., 89*, 209-222.
Lomo, T., Westgarrd, R. H. & Kahl, H. A. (1974). Contractile properties of muscle: control by pattern of muscle activity in the rat. *Proc. Roy. Soc. Lond.* (B), *187*, 99-103.
Madhani, H., Bohr, V. and Hanawalt, P. (1986). *Cell, 45*, 417.
Mason, R. J. & Rose, S.P.R. (1986). Lasting changes in spontaneous multi-unit activity in the chick brain following passive avoidance training. *Neuroscience*, (in press).
Matsuda, R. (1982). The evolutionary process in talitrid amphipods and salamanders in changing environments, with a discussion of 'gene assimilation' and some other evolutionary concepts. *Canad. J. Zool., 60*, 733-749.
Maynard-Smith, J. & Holliday, R. (Eds.). (1979). *Preface to the evolution of adaptation by natural selection.* London: The Royal Society.
McClintock, B. (1984). The significance of responses of the genome to challenge. *Science, 226*, 792-801.
Opadia-Kadima, G. Z. (1987). How the slot machine led biologists astray. *J. theor. Biol.*, (in press).
Oyama, S. (1986). *The ontogeny of information*, Cambridge: Cambridge Univ. Press.
Packard, A. *The role of behaviour in evolution: a metaselection theory.* Unpublished preprint, 1986.
Plotkin, H. C. (1982). *Learning, development and culture*, London: Wiley.
Pollard, J. W. (1984). Is Weismann's barrier absolute? In M. W. Ho & P. T. Saunders (Eds.), *Beyond neo-Darwinism: an introduction to the new evolutionary paradigm.* London: Academic Press.
Pollard, J. W. (1987). The fluid genome and evolution. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metaphors.* London: Wiley.

Robertson, M. (1984). Receptor gene rearrangement and ontogeny of T lymphocytes. *Nature, 311*, 305-306.
Rose, S.P.R. (1986). Neural mechanisms of memory. In D. Alkon & G. Woody (Eds.), *Neural mechanisms of conditioning.* New York: Plenum Press.
Saunders, P. T. (1980). *An introduction to catastrophe theory*, Cambridge: Cambridge University Press.
Saunders, P. T. (1984). Development and evolution. In M. W. Ho & P. T. Saunders (Eds.), *Beyond neo-Darwinism: an introduction to the new evolutionary paradigm.* London: Academic Press.
Saunders, P. T. (1987). Sociobiology—a house built on sand. In M. W. Ho & S. W. Fox (Eds.), *Evolutionary process and metaphors.* London: Wiley.
Schneirla, T. C. (1966). Behavioural development and comparative psychology. *Quart. Rev. Biol., 41*, 283-302.
Sinha, C. A. (1984). Socionaturalistic approach to human development. In M. W. Ho & P. T. Saunders (Eds.), *Beyond neo-Darwinism: an introduction to the new evolutionary paradigm.* London: Academic Press.
Skinner, B. F. (1981). Selection by consequences. *Science, 213*, 501-504.
Skinner, B. F. (1984). Author's response: representations and misrepresentations (Open peer commentary of 'behaviourism at fifty'). *Behav. Brain Sci., 7*, 655-667.
Skinner, B. F. (1985). News from nowhere, 1984. *The Behavior Analyst, 8*, 5-14.
Soares, M. B., Schon, E., Henderson, A., Karathanasis, S. K., Cate, R., Zeitlin, S., Chirgwin, J. & Efstratiadis, A. (1985). RNA-mediated gene duplication: the rat preproinsulin I gene is a functional retroposon. *Mol. Cell. Biol., 5*, 2090-2103.
Temin, H.M. (1971). The protovirus hypothesis: speculation on the significance of RNA-directed DNA synthesis for normal development and for carcinogenesis. *J. Nat. Cancer. Inst., 46*, III-VII.
Temin, H. M. & Engels, W. (1984). Movable genetic elements and evolution. In J. W. Pollard (Ed.), *Evolutionary theory: Paths into the future.* London: Wiley.
Thom, R. (1975). *Structural stability and morphogenesis*, Reading, Mass.: W. A. Benjamin, inc.
Thompson, D'Arcy, W. (1917). *On growth and form*, Cambridge: Cambridge University Press.
Tobach, E. & Greenberg, G. (Eds.) (1984). *Behavioral evolution and integrative levels.* New Jersey: Lawrence Erlbaum Associates.
Watson, J. D., Tooze, J. & Kurtz, D. T. (1983). *Recombinant DNA, A short course.* New York: Freeman.
Winfree, A. T. & Strogatz, S. H. (1983). Singular filaments organize chemical waves in three dimensions. I. Geometrically simple waves. *Physica, 8D*, 35-49.