

# Non-Darwinian "evolution" and biological progress

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*The use of terms such as "higher" and "lower" to describe different forms of life shows that we tend to think of evolution not only as adaptive, but also in some sense as progressive. That sense can be defined in a way that makes it possible to show how some "neutral" polymorphisms could contribute to progressive evolution.*

PROGRESS and its adjective progressive are ambiguous words. They may imply merely unidirectional change, or they may imply change in a direction that is regarded as improvement. They have been used in both senses (sometimes both senses are confounded) in writings about evolution, but though there have been difficulties in defining progressive evolutionary change in the sense of improvement, many authors have clearly felt that evolutionary changes have given rise to improvement. Indeed most feel so: otherwise the use of higher and lower as applied to various animal and plant groups would be seen to be empty of meaning.

Some time ago<sup>1,2</sup>, I made an attempt to define "biological progress" in a way that I thought avoided the circularity of the arguments that had been used by Julian Huxley<sup>3,4</sup> whose definition of progress was based on the implicit assumption that progress has in fact occurred. Stebbins' recent book<sup>5</sup> also makes this implicit, and it seems to me, unwarrantable assumption.

My attempt avoided this assumption by defining progress solely in terms of the general conditions of survival. Most of the trends Huxley and Stebbins identified as progressive fall into progress as I defined it either under the headings of phenotypic flexibility (see below) or environmental control.

Current controversy about the role of neutral alleles in evolution prompts me to consider to what extent such neutral alleles may contribute to progressive evolution as so defined.

## Neutral alleles and adaptive evolution

The controversy concerning neutral alleles centres on the question of the proportions of genetic differences produced by mutation that can be regarded as selectively neutral, and on the extent to which such spread of neutral alleles may explain differences between populations and species and also explain the number of alleles at a locus to be found in a population. Since the spread of neutral alleles is a purely chance process, such evolution has been called non-Darwinian<sup>6</sup>.

The theory of evolution has two major components, the concept of evolution itself and the mechanism of change that has brought evolution about.

The concept of evolution explains the classifiability of

organisms, the facts of plant and animal geography, the common behavioural, morphological, embryological, anatomical, physiological, biochemical, cytological and genetic properties of diverse organisms, the facts of palaeontology and palaeobotany, results of the study of microevolution in "nature" and in the laboratory, and the results of plant and animal breeders. It does so by postulating that diversity is the consequence of modification over the generations of differing lines descended from common ancestors. It does not explain adaptations as such but explains the diversity of adaptations.

Our concepts of the mechanism of evolution seek to explain the change that gave rise to this diversity of adapted organisms, and here it is essential that an evolutionary theory must explain adaptedness and changes of adaptive mode. Natural selection is the agent central to Darwinian evolution because it explains adaptedness. Modern Darwinian theory has the following components: mutation, random with respect to place, time and need, which provides the source of allelic heterogeneity that is the basis of change; segregation and recombination that provide varying combinations of alleles and diversity of genotypes; selection which increases the relative frequency of the genotypes that on the average lead to the fitter (relatively better adapted) phenotypes; and genetic drift which leads to random changes in allele frequency and in small populations may establish an allele in a population sometimes even if that allele leads to phenotypes less fit than some alternative allele and which will certainly establish neutral alleles. Those of strong selectionist views would allow only a very minor role for drift, except in its special forms of "founder principle" and when there are very restricted bottlenecks in population size.

Non-Darwinian evolution, on the other hand, would give drift a major role in molecular evolution by postulating that a large proportion of mutations leads to neutral alleles, that is to say to alleles that do not differ in their effect on fitness from the alleles that mutated. L 7

Two interesting points emerge. One is that these new developments would greatly increase the role of chance in the determination of the direction of evolution. Darwinian evolution involves considerable elements of chance, not only with respect to drift, but also to the timing and direction of mutation and the chance involved in the origin of particular combinations of genes. It is of interest here to draw attention to the fact that it is this chance component of evolutionary theory to which many (see for example ref. 7) object, with its consequences that the precise course of evolution is unpredictable, that evolution could have

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taken many other paths, that any particular species or individual must be regarded as an accident, and that evolutionary changes are not necessarily either adaptive or progressive; these are aspects of the theory that do not conform with any of our fundamental philosophies or with our egocentric outlook. Non-Darwinian evolution would simply add a greater component of chance.

The second point is that in so far as substitution of neutral genes by chance processes is regarded as "evolution" it must be questioned whether the "evolution" it considers is the same as "evolution" considered in the Darwinian sense.

Population geneticists have come to talk of changes of allele frequencies as evolution. But evolution, in the classic sense, involves adaptive changes of phenotype. Neutral allele substitutions cannot be adaptive, and, from the point of view of adaptive evolution theory, it seems doubtful whether a genotypic difference which can never make any difference to fitness is to be regarded as relevant. The relevance to adaptive evolution of a genotypic difference which makes a difference that we can detect at some level we call phenotype, but which makes no difference to the economy of the organisms, is questionable.

In discussing whether "neutral" alleles might in any sense be relevant to adaptive evolution we must therefore consider the kinds of neutral allele pairs we may envisage. There are four, of which we shall see that only two, conditionally neutral and pseudo-neutral allele pairs, can be envisaged as playing any role in adaptive evolution.

### Strictly neutral allele pairs

These are pairs of alleles that can in no circumstances make any relative difference to fitness and therefore can in no circumstances contribute to adaptive or progressive evolution. They may include redundant codon differences, though it should not be forgotten that these might differ in efficiency of transcription or replication, and that some redundant codon pairs may involve some recombinational load, for example UUA and CUU both code for leucine but can recombine to give UUU phenylalanine.

They may also include allele pairs that are meaningful codon differences but lead to "redundant" amino acid substitutions in parts of a protein that do not affect the protein's function. Some of these differences may be detectable by techniques other than sequencing, for example tests of electrophoretic mobility, heat stability, enzyme activity, and thus have some detectable effect on some aspects of phenotype, but might nevertheless have no effect on fitness. It seems fair to suggest that the more readily detectable at such levels the differences are, the more likely they are to affect fitness.

Among these differences there may be some that have an overt effect on gross phenotype. The history of population genetics, in which one after the other overt polymorphism has been claimed to be neutral but has subsequently been proved to be maintained by selection, should lead to some scepticism concerning this possibility.

### Quasi-neutral allele pairs

These have been proposed by Kimura, and the proposition might be regarded as a retreat from the more strictly neutralist position though he originally<sup>8</sup> did refer to "neutral or nearly neutral" alleles. They are alleles that affect fitness, but do so to such a small extent that their fate can be accurately predicted by neutral theory. Unless, however, their negligible effect on fitness can change (in which case they are conditionally neutral, see below) they are as unlikely to be relevant as strictly neutral alleles.

### Conditionally neutral allele pairs

These are allele pairs that were neutral or quasi-neutral in past circumstances but may be non-neutral in some future genetic or external environmental circumstance. To separate these as a category is important for they may be envisaged as a class of neutral alleles that may be established and maintained in a population without affecting fitness, but in some other circumstances might form a source of genetic variance that through selection could improve adaptedness.

As an illustrative model example we might envisage a pair of alleles differing in the heat stability of the enzyme they code for: say that one enzyme is inactivated at 33 °C, the other at 40 °C. Assuming that, below the critical temperature 33 °C, the isoenzymes have the same biochemical properties, and also assuming that the environment of the population never involves temperatures higher than this, the alleles will be neutral. But if the environment changes, or if some part of the population migrates to some new area, by accident or as a result of change elsewhere in the genome that enables the population to spread out of its hitherto restricted range, so that temperatures above 33 °C are now met, then the alleles cease to be neutral and natural selection will begin to affect their frequencies. The conditionally neutral polymorphism might then be said to be preadaptive.

### Pseudo-neutral allele pairs

These are of two kinds. The first are similar to conditionally neutral alleles. They are those which were in the past non-neutral but, because conditions have changed, are neutral now. They must of course contribute to the pool of conditionally neutral alleles now since the change of conditions might be reversed, but they must be distinguished because their presence in the population is a result of selection so that they, being neutral now, will contribute to the difficulty of determining what proportion of molecular polymorphism results from non-Darwinian evolution.

The second are alleles which are neutral or quasi-neutral in present circumstances because selection has made them so. Among these we include those showing frequency dependence, for by definition these at equilibrium are neutral, but their neutrality is itself a consequence of selection. Cyclic selection, niche-dependent disruptive selection, especially with habitat choice<sup>9</sup>, and density dependent selection may all contribute to such pseudo-neutrality. Balanced polygenic systems as envisaged by Mather would also involve pseudo-neutrality, the relative fitness effects of alleles at the separate loci being neutralised by their balancing with alleles of opposite effects in linked loci. Modifiers may fall into this category also.

There is good evidence that some molecular differences are subject to such frequency dependent selection. (See Kojima and Yarbrough<sup>10</sup> for direct frequency dependence, Powell<sup>11</sup> or Ayala<sup>12</sup> for niche-dependent disruptive selection.) Furthermore we have no reason to suppose that many of the molecular differences we can detect by such techniques as electrophoresis are not part of polygenic systems, just as may be differences in reiterated DNA.

Pseudo-neutral genes are clearly subject to Darwinian evolution.

### Neutral alleles and progressive evolution

In considering the possible contribution of neutral alleles to progressive evolution we must have in mind the changes that fall under the definition of progressive changes.

To survive, in anything but the short term, a population or species must have in sufficient measure each of

three properties, adaptedness, stability and variability.

These three concepts express the three basic conditions of continued life, and two of them, genetic stability and variability, are in part antithetic, for they express the need to maintain present adaptedness through stable heredity, but at the same time to preserve adaptability to future different environments.

It needs to be stressed first that we are by no means solely concerned with inorganic sources of environmental change, for evolutionary change of one species is an important environmental change for others that interact with it. Second that, at least from the point of view of the organisms, future environmental change, and hence the adaptation that will be required, is unpredictable. Adaptation to the unpredictable requires the generation of variance at random<sup>13</sup>, but to generate variance at random necessarily involves a reduction of genetic stability. We can therefore see that progressive evolution must be evolution that leads either to a reduction in the need to generate random variance, or to the storage of such variance in temporarily ineffective forms.

In my original discussions of this concept of progress<sup>1,2</sup>, I pointed to various ways in which these ends have been achieved. These can be summarised under the headings of the various components of long term fitness as follows.

(1) Adaptedness: this expresses the degree to which individuals fit contemporary environments, and within populations relative adaptedness is equivalent to Darwinian fitness. When we are comparing species or major groups, however, since most of them survive well in their contemporary environments, we cannot look to adaptedness in this sense when looking for evidence of progressive evolution.

(2) Genetic stability: this expresses the capacity of individuals to produce adapted offspring, and is promoted by asexual reproduction, inbreeding, homozygosity, and low mutation rates.

(3) Variability: this expresses the capacity of a population to change and depends on (a) genetic flexibility, which is the capacity of the population to produce offspring different from their parents, and is promoted by high mutation rates, heterozygosity and outbreeding; and (b) phenotypic flexibility. Phenotypic flexibility expresses the range of environments in which the individual can function, or the ability of the individual to "recognise" and move from unfavourable to favourable environments. It is this component of fitness that covers most of the progressive trends recognised by Huxley<sup>3</sup> as making organisms relatively independent of the environment, or rather of certain aspects of environmental variation. Some would include phenotypic flexibility as part of adaptedness, but I separate them because such flexibility is part of adaptability. Recent developments show that relatively "simple" organisms have more phenotypic flexibility than might hitherto have been thought for the gene control systems of, for example, *E. coli*<sup>4</sup> or *Aspergillus nidulans*<sup>5</sup> provide efficient biochemical flexibility allowing the individual to adapt to variation in the external environment.

(4) Stability of environment: this determines the need for change which can be reduced by (a) specialisation for stable components of environment, a risky process because the continued stability of the habitat is unpredictable, and (b) control of environment directed towards maintaining its suitability, or making it more suitable and keeping it so.

It is the changes that may lead to partial resolution of this antithesis between the requirements of stability and variability that we must define as progressive changes. The antithesis lies between genetic stability and genetic flexibility and is resolved by any increase of phenotypic flexibility, by the adoption of a stable habitat, or of environmental control (which requires the development of communities and, in the ultimate, ability to predict in order to correct environmental trends).

These are ways that reduce the need for genetic flexibility. But the direct antithesis between genetic stability and genetic flexibility has also been reduced by two developments, and may possibly have been reduced by a third.

The first is through the adoption of dual breeding systems, asexual reproduction providing stability and sexual reproduction providing flexibility.

The second is through the development of genetic systems that permit the storage of potential variation<sup>16,17</sup> without consequent variation of fitness. Such storage is achieved through dominance in diploids, the heterozygous recessives being a source of variance that is "hidden". In diploids and haploids, balanced polygenic systems provide a source of stored potential variation. In outbreeding populations the fixed variation is freed at a rate determined largely by recombination. In inbreeders, complementary alleles may be fixed in different more or less homozygous lines, and the freeing of this variation depends on the frequency of hybridisation (outbreeding) between such lines and on the subsequent recombination in the hybrids. Recombination frequencies are of course also under genetic control, which may perhaps be relaxed in unfavourable circumstances, after wide outcrossing, or as a result of intensive selection, so that the rate of release of potential variation may itself be increased when genetic flexibility is most needed.

The third possibility is that in unfavourable circumstances the control of replication, including DNA repair systems, may be impaired, thus leading to increase in mutation rate when genetic flexibility is most needed<sup>18</sup>.

It is clearly in respect to the resolution of this antithesis between genetic stability and genetic flexibility, that neutral allele polymorphisms might be important.

Strictly neutral allele pairs clearly make no contribution to short term or long term fitness, and if they exist they are mere evolutionary noise.

On the other hand those conditionally neutral allele pairs that have been established in populations by non-Darwinian evolution, but may in some future conditions cease to be neutral, provide in principle a potential source of genetic flexibility that does not involve loss of genetic stability. They thus provide an additional source of stored potential variation. Polymorphisms for such conditionally neutral alleles may therefore provide a source of adaptation to the unpredictability of the environment. If so, non-Darwinian evolution is an additional source of evolutionary progress.

I conclude that neutral allele pairs can only contribute to evolution in the classic sense, as distinct from evolution defined as mere gene frequency change, if the neutrality is "conditional". The establishment of unconditionally neutral alleles is mere evolutionary noise. The establishment by "non-Darwinian evolution" of polymorphisms for neutral alleles which may in future combinations or conditions cease to be neutral may provide an important source of genetic flexibility that does not impair genetic stability. The establishment of such polymorphisms would be an additional form of progressive evolution.

- 1 Thoday, J. M., *Symp. Soc. exp. Biol.*, 7, 96-113 (1953).
- 2 Thoday, J. M., in *A Century of Darwin* (edit. by Barnett, S. A.), 313-333 (Heinemann, London, 1958).
- 3 Huxley, J., *Evolution* (Allen and Unwin, London, 1942).
- 4 Huxley, J., *Evolution and Ethics* (Pilot Books, New York, 1947).
- 5 Stebbins, G. L., *The Basis of Progressive Evolution* (University of North Carolina Press, Chapel Hill, 1969).
- 6 King, J. L., and Jukes, T. N., *Science*, 164, 788-798 (1969).
- 7 Koestler, A., *The Case of the Midwife Toad* (Hutchinson, London, 1971).
- 8 Kimura, M., *Nature*, 217, 624-626 (1968).
- 9 Thoday, J. M., *Proc. R. Soc.*, B182, 109-143 (1972).
- 10 Kojima, K. I., and Yarbrough, K. M., *Proc. natn. Acad. Sci. U.S.A.*, 57, 645-649 (1967).
- 11 Powell, J. R., *Science*, 174, 1035-1036 (1971).
- 12 McDonald, J. F., and Ayala, F. J., *Nature*, 250, 572-574 (1974).
- 13 Thoday, J. M., *Theoria to Theory*, 2, 29-38 (1967).
- 14 Jacob, F., and Monod, J., *J. molec. Biol.*, 3, 318-356 (1961).
- 15 Cove, D. J., and Pateman, J. A., *Nature*, 215, 1234-1237 (1967).
- 16 Mather, K., *Biol. Rev.*, 18, 32-64 (1943).
- 17 Mather, K., *Genetical Structure of Populations* (Chapman and Hall, London, 1973).
- 18 Sturevant, A. H., *Proc. natn. Acad. Sci. U.S.A.*, 25, 308-310 (1939).