Speculations on the transfer of heritable information by general causal cycles

David O. F. Skibinski[1]

[1]Swansea University

April 28, 2020

Abstract

The mode of inheritance and evolutionary consequences of heritable information associated with general causal cycles is discussed. It is suggested that the importance of such information may have been underestimated particularly as a cause of morphological differences between species. The problem of obtaining evidence for these speculations is considered.

Publication Note

This preprint is from the author's post-print of the article:

Skibinski, D.O.F., *Speculations in Science and Technology, 8*, (1), 51-60 (1985). ISSN 0155-7785

This journal was discontinued in 1999, and the article has not been available online.

d.o.f.skibinski@swansea.ac.uk

Introduction

While it is now accepted that nuclear and organelle DNA provide the main source of heritable information in living organisms, additional extranuclear sources of information have been recognised.[1] This paper speculates on the properties and evolution of one of these alternative forms: information transmitted over generations by general causal cycles. To begin, a criterion for heritable information will be considered, followed by a brief review of known sources of heritable information.

An experimentally useful criterion is that heritable information exists for any attribute of a living organism in which a change can be inherited in the absence of its cause. Structural changes in germline DNA can be passed to future generations and thus fulfil the criterion: most externally caused phenotypic changes clearly do not. The qualification in the criterion concerning the absence of cause excludes changes confounded with environmental correlation between relatives and is of crucial importance in experimental attempts to demonstrate the inheritance of acquired characters. The criterion has a defect in that it excludes certain attributes against common sense, e.g. DNA sequences in which only dominant lethal changes can occur. An appeal to analogy might however be made in such situations.

Nucleic acid is an ideal hereditary material both for stability of information storage and ease of duplication and repair. From the viewpoint of information theory[2,3] biological organisms are exceedingly complex and perhaps only nucleic acid can store efficiently the required large quantities of information. This may be true for molecular coding but morphological differences as between species may be achieved by simple transformations of scale[4] and little information may be required to direct early egg development.[5] It is also difficult to sustain the argument that efficient storage is important when much DNA in higher organisms is non-coding.

An advantage of molecular information storage is the resistance provided against thermodynamic decay.[6] Heritable information could however be stored in any phenotypic attribute for example in the activity of molecules in a cell or the numbers or sizes of cells or organs provided that mechanisms exist for duplication and transmission. In fact the effects of polyploidy are the result of an inherited change in number of chromosomes rather than molecular structure.

Evidence now exists for evolutionary important types of heritable nucleic acid change other than those of base substitution, rearrangement and ploidy changes. Gene conversion and unequal crossing over, for example, may be important not only in the concerted evolution of multigene families but also in speciation and phenotypic trends.[7] Another mechanism involving the capture of mRNA by endogenous RNA viruses followed by transfer of the information to germ line DNA after reverse transcription has been proposed to explain the inheritance of acquired immunological tolerance.[8] This mechanism was extended as a general theory of evolution in which clonal selection and amplification of particular genes and mRNA species precedes transfer of the amplified information to the germ line.[9] The theory, permitting inheritance of acquired adaptations, has however not been well corroborated even in the special case of immunological tolerance.[10] It does involve transient information storage in numbers of particular cell types and RNA species before fixation in the structure of germline DNA.

Examples of heritable information storage in structure other than nucleic acid include the inheritance of changes in the cortex of *Paramecium aurelia*[11] and other ciliates and in the cell wall of *Bacillus subtilis*.[12] Phenomena similar to those observed in ciliates may also occur in the cortex of eggs.[13] Evidence of information storage in molecular activity or concentration rather than structure include induction phenomena such as the galactosidase permease system in *E. coli*[14] where either of two alternative stable steady states may be inherited to an extent independently of external inducer concentration. Mathematical analysis demonstrates that these properties can be explained by feedback systems.[15,16] Other inherited phenomena which may involve feedback mechanisms or stable association of macromolecules with germline DNA include serotype transformation in *Paramecium*,[17] environmentally induced changes in flax[18] and tobacco,[19] inheritance of the scrapie agent[20] and extinction phenomena in rotifers.[21] It must be emphasised that by the criterion of heritable information the alternative states of an operon system store information in addition to that stored in the nucleic acid sequences involved in the feedback circuitry.

Information storage in cycles

The idea of information storage in cyclical sequences of events dates back to the theory that cycles of enzyme catalysed reactions could explain the inheritance of induced metabolic states in bacteria.[22,23] It is the aim of this paper to extend the idea to the storage of information in general causal cycles. The potential of cycles for information storage will be considered and speculation will be made on their possible role and importance in evolutionary change.

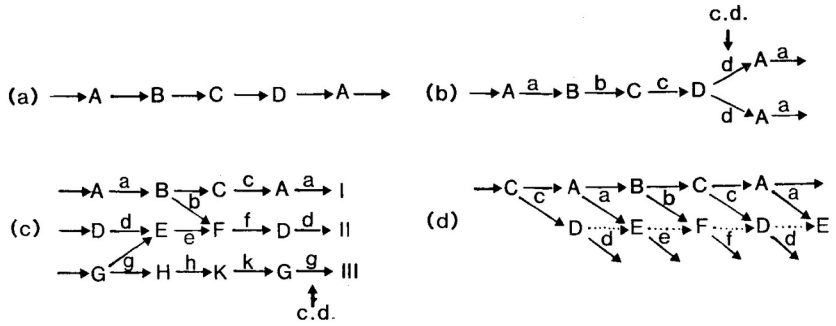

Figure 1: Examples of cyclic sequences: (a) a general causal cycle; (b) a cycle of four genes A, B, C and D with gene products a, b, c and d; (c) a network interpretable as three cycles *I, II, III* with interconnecting causal links; (d) mechanism for the evolution of new cycles. (c.d. = cell division)

A general causal cycle of events is represented in Figure 1(a). In this sequence A causes B which in turn causes C which causes D. Finally D causes event A completing the cycle. A biological application of this model is given in Figure 1(b). This represents four genes, A, B, C and D, of a single-celled organism with RNA or protein gene products a, b, c and d. Gene product a switches on gene B which produces gene product b; b switches on gene C and so on until gene A is switched on again to give product a. Negative feedback effects on synthesis, or dilution, or breakdown of a gene product could prevent its accumulation and thus ensure a true cycle. The period, or time between successive events of the cycle need not be constant if switching also depends on other external or internal forces. In Figure 1(b) the period of the cycle is kept in phase with the cell cycle by assuming that cell division is necessary for synthesis of a. Causal cycles analogous to that of Figure 1(b) are characteristic of living systems where for example the cell cycle consists of a number of distant sequential stages. Figure 1(b) illustrates a general principle, and fewer or more steps in the cycle could be envisaged with other forms of molecular interaction. The cycle of Figure 1(b) stores heritable information apart from that encoded in the genes A, B, C and D, because an external environmental factor or adaptive phenotypic response suppressing synthesis of say gene product b would terminate the sequence of switching events. The cycle would be broken and the phenotype associated with gene products a, b, c and d would be lost. There would be two heritable alternatives, 'cycle on' and 'cycle off' and switching between them achieved by external factors. The cycle might also be broken by a gene mutation and the 'cycle off' alternative could be lethal. Cell cycle events are obviously more complex than those of Figure 1(b) and perhaps form a network of interacting events. Possible implications of increased complexity are shown in Figure 1(c). Here a network of events can be interpreted as three separate cycles, *I*, *II* and *III*. The cycles show inter-dependence because gene products b and g are involved in switching events in more than one cycle. In this situation inhibition of an event in one cycle may subsequently break other cycles. Conversely a break in one cycle may be repaired by later switching on of the cycle by events in other cycles. This is summarised in Table 1 which gives the phenotypes just before cell division resulting from breakage of cycles *II* and *III* by inhibition of synthesis of c, f or k within one cell generation.

Gene Products		Cycle broken		
Necessary	Sufficient	I	II	III
All		G	A, G	A
-	All	D, G	A, D, G	A, D
b	Remainder	G	A, D, G	A, D
g	Remainder	D, G	A, D, G	A

Table 1: Effect of cycle breakage on phenotype for the network of Figure 1(c). Phenotypes are represented by whichever of the genes *A, D,* or *G* are switched on just prior to cell division. Absence of a necessary gene product takes priority over presence of a sufficient gene product.

Shown separately are the phenotypes resulting when the presence of *b* and *g* are necessary or sufficient conditions for switching genes *E* and *F*. The results show that a variety of different phenotypes can be obtained by phenotypic changes affecting a single cycle and that sufficient causes tend to protect the network system against phenotypic changes associated with cycle breakage, while necessary causes have the reverse effect. A mechanism for the addition of a new cycle to a pre-existing network is shown in Figure 1 (d). Gene products *a*, *b* and *c* switch on genes *D*, *E* and *F* which are not part of a cycle. These switches could have arisen by genetic assimilation[24] of adaptive responses associated with the production of *d*, *e* and *f*. In this situation selection might then favour genetic changes which ensure switching of genes *D*, *E* and *F* by interaction between *d* and *E*, *e* and *F* and *f* and *D* as indicated by dotted arrows in Figure 1(d). This would add a new cycle which could be broken independently of the cycle *A-B-C-A* if *d*, *e* and *f* become necessary for switching genes *E*, *F* and *D*. In this way a network of cycles as in Figure 1(c) could be built up by selection.

In multicellular animals greater possibilities exist for cycles than in single celled organisms, particularly in the female line. Figure 2 symbolises the association between maternal and offspring phenotype and germline. Three types of cycle are represented as dotted lines marked with arrows; letters are omitted. Cycle *I* is confined to the germ cell line representing the phenomena discussed in relation to Figure 1.

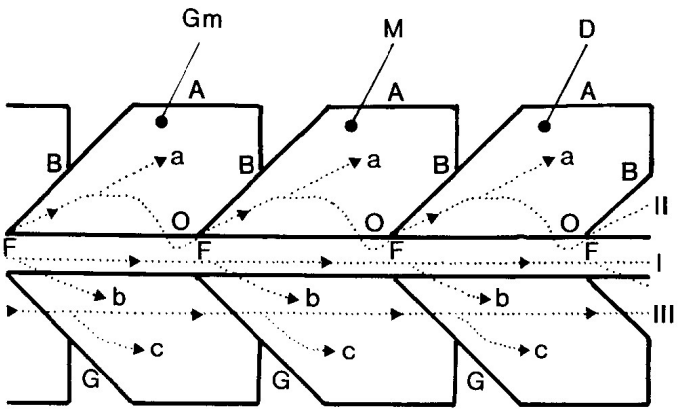

Figure 2: Symbolic representation of association between maternal and offspring phenotype and germline in a line a descent. Dotted lines indicate cycles *I, II*, and *III* with branching sequences *a, b*, and *c*. A, adult; B, birth; F, fertilization; O, oogenesis; G, growth; Gm, grandmother; M, mother; D, daughter

In most animals the early stages of development are directed by maternal factors localised in the egg during oogenesis. This phenomenon of localisation results at the end of cleavage in a group of cells whose subsequent development depends on the part of the egg cytoplasm they have inherited.[25] Cleavage may also occur in achromosomal eggs.[26] Centrifugation of eggs before cleavage can cause redistribution of cytoplasm and abnormal embryos.[27] Furthermore zygotic genes are rarely involved in early morphogenesis.[28] This raises the possibility of the phenomenon of cycle *II* where the cycle is localised partly in the mother and partly in the oocyte, egg and developing embryo. Finally, it is known in mammals that the growth of the developing embryo before birth is influenced by the mother, through nutritional effects for example.[5] These possibilities are represented by cycle *III* which is localised entirely outside the germ line. The events of these cycles may be mediated by molecular interactions acting at transcription or translation, by hormones or even mechanical or electrical forces. Figure 2 also shows non-cyclic branching sequences *a*, *b* and *c* involved in ontogenesis and normal adult function and which may as in Figure 1(d) evolve to give new elements to a cyclic network. In iteroparous animals such as mammals repeated ovulation could be triggered by epicycles which provide a necessary cause for continuance of the main cycles.

If non-genetic heritable information can become associated with a network of cycles built up by genetic evolution, subsequent changes in this information might seem to be largely degenerative involving cycle breakage. Another type of information may however be associated with a network. Suppose that in Figure 1(b) an increase in the intracellular activity of a occurs as an adaptive phenotypic response. If the rate of synthesis of b is kinetically dependent on the activity of a, the activity of b will increase. Thus, in turn, around the cycle, the activities of c and d will also increase, finally reproducing an increased activity of a in the next generation, without the necessity of the original adaptive stimulus. In the model of Figure 1(c) such changes might be transmitted, dispersed or amplified through a network of cycles. In multicellular organisms, cell multiplication or selection among somatic cell lines might also result in increases in the activity of signals within a network of cycles which could be transmitted to future generations. This additional source of heritable information has interesting consequences. First, stochastic development forces acting within female lines of descent might generate heritable variation on which directional selection could act; stabilising selection might also constrain variation between lines. Second, the inheritance of acquired adaptations could occur but unlike the somatic selection hypothesis[19] information underlying the changes would not be passed to germline DNA. Third, the strength of causal signals in a network might be amplified over generations causing a phenotypic trend which, as with molecular drive,[7] could occur in the face of natural selection. This would require simultaneous changes, resulting perhaps from climatic change, in all lines of descent to

keep heritable variation between lines low. The mechanism could account for apparently maladaptive fossil trends.

Phenotypic information

Although the existence of cycles depends on nuclear gene activity cycles provide an additional source of heritable information. How by the criterion of heritable information is this additional information stored? Consider the synthesis of gene product a in Figure 1(b). At this point in time certain changes in magnitude in the activity of a can be transmitted by the cycle. It is convenient therefore to regard information as being stored in the value of the activity of a and transmitted to the next generation by the cycle. This storage is transient as the information is passed to the activity of b then c around the cycle. In multicellular organisms the same principle applies, the information being stored transiently in attributes such as intracellular concentration, cell number, body size and transmitted by a cycle. I propose to call this information 'phenotypic information' to emphasise its association with phenotypic attributes outside the germline, and to distinguish it from other sources of extranuclear information. Phenotypic information may also be nuclear if it is stored partly in the form of more or less stable associations between germline DNA and other macromolecules. It may be noted that reproduction of all information, for example nucleic acid replication, may be interpreted as a cyclic process but that not all cyclic processes store phenotypic information. The distinction between structure, steady states, or cycles may not always be clear cut as may be the case with information stored in the cortex of ciliates or eggs.

The problems of evidence

The idea of the association of information with cyclic processes is not new and often alluded to in genetic texts. It is the aim of this paper to develop the idea explicitly to the extent now of speculating that phenotypic information may have an important role in evolutionary change.

Classical genetic analysis does not pinpoint all the heritable causes involved in the ontogenesis of a character. For example, some genes may be of such crucial importance for normal development that alternative forms are lethal. Conversely some characters particularly those determining the major morphological features of a species may be invariant. Thus, the existence of substantial genetic variation for a character does not exclude the influence of other heritable causes such as phenotypic information.

It is thought that the evolution of gross morphological differences between species arise from mutations in control genes rather than the evolution of new proteins.[29] Consideration of the theoretical properties of phenotypic information suggests that it might play a similar role to control genes. It does however depend on nuclear gene activity and should be regarded as an additional rather than alternative source of information.

As to the question of direct evidence, I suggest that there are few experimental observations which provide clear answers one way or the other. Two main approaches can be considered.

First, attempts could be made to demonstrate heritable changes after physical manipulation or induction of adaptive phenotypic responses. Evidence for the inheritance of acquired characters has been elusive and it is difficult to exclude the genetic effects of selection, inbreeding or segregation.[30] Traditional scepticism partly reflects the absence of a theoretical framework that phenotypic information and indeed the somatic selection hypothesis provide. Some more specific predictions can be made for phenotypic information; first the inherited effect may not be identical to the inducing phenotypic alteration, and second the alteration must occur before the phenotypic information is transmitted to the next generation.

A second approach to evidence is through the study of maternal influences. The complex role of the mother in phenomena such as localisation is consistent with the view that heritable information is associated with these maternal properties.[5] A cyclic network could be required for setting up this complexity but if the network

has a high density of interconnecting 'sufficient' causal links it will have considerable homeostatic power in repairing broken links. Thus although maternal influences may provide information crucial for development they do not necessarily store heritable information. This point is relevant when considering reciprocal phenotypic differences occurring frequently in species crosses. In order to demonstrate extranuclear inheritance it is necessary to replace, by backcrossing, the nuclear genes in the maternal line of one species with those of the other. This has been done in plants,[31] but hybrid reproductive problems cause difficulties in animals. Such an experiment may however be able to distinguish between phenotypic information and other types of extranuclear inheritance. Thus, if cycles are broken by foreign nuclear genes in the backcross programme, phenotypic information would be lost but not necessarily restored by reversing the backcross programme and reinserting the original nuclear genes. Information stored in autonomous replicating structure is less likely to be affected in this way. Nuclear transplantation provides an alternative to backcrossing and an experiment involving two *Amoeba* species[32] provides relevant results. Reciprocal nuclear transplants between species were made into enucleated cytoplasm, and hybrid populations were obtained resembling the nuclear parent biochemically and the cytoplasmic parent in morphological characters such as cell shape. Back transfers of nuclei produced phenotypes different from those of the original parents. These results are consistent with cycle breakage during the whole transfer process. Reciprocal differences have also been observed in interspecific nuclear transplants in multicellular animals, for example frogs and toads.[33] Unfortunately, as with crosses, hybrid embryos usually die at an early stage, preventing demonstration of extranuclear inheritance. Reciprocal nuclear transplants have been made between two species of *Xenopus* and hybrid embryos raised to fertile adult frogs.[34] These frogs and their offspring resembled the subspecies providing the nucleus. This suggests that phenotypic information is not involved in determining the subspecific differences, although rare hybrids intermediate between nuclear and cytoplasmic parents were found. Also as maternal effects were not present the cross would not have been chosen *a priori* in an investigation of extranuclear inheritance. Experiments of this kind do however provide possibilities for corroborating or refuting ideas concerning phenotypic information.

Totipotency of adult cells as observed in plants is on the whole not consistent with an important role for phenotypic information but where it exists in animals totipotency is usually lost after a few egg divisions.

Applications of the concept of phenotypic information

To conclude, several problems to which the concept of phenotypic information can be applied will be discussed.

The first concerns the life cycle, which is undoubtedly a sequence of causes and events dependent on gene activity. Genetic changes alone however, may be insufficient to explain the cycles' existence or creation. This may be seen by considering the following paradox similar to that of the 'chicken and egg'. It is that the cycle cannot be switched on unless gene products are available: but gene products cannot be produced unless the cycle is switched on. The paradox can be solved by assuming that the first synthesis of gene products occurred in response to an environmental stimulus and that this acquired phenotypic change was transmitted by the cycle and inherited by future generations. The phenotypic information may not now be identifiable experimentally because of lethal effects of cycle breakage.

A second phenomenon is the inheritance and evolution of asymmetrical phenotypic bias in animals. For most characters artificial selection is effective indicating the underlying presence of genetic variation.[35] For asymmetrical bias this is not so; artificial selection is slow or ineffective and heritability low.[36] Moreover there appear to be no instances where either the direction, or presence or absence of bias in an individual is determined by its own genotype.[37] It is difficult in fact to imagine how a genetic change in a bilaterally symmetrical organism could induce bias since both sides must inherit the change and should react identically to it. A mechanism is needed to provide different positional information[38] to the two sides. This can be achieved if bias is caused by a left-right gradient produced in the egg cytoplasm, or in the early stages of embryogenesis.[37] Spatial anisotropy may also be required in the egg to provide positional information for

the rostro-caudal and dorso-ventral plane but any simple mechanism of setting up gradients *de novo* may suffice for this. The problem with asymmetry is to consistently define a left or right bias.

A left-right egg gradient could be set up in two ways, as a result either of biased maternal gene action or influences, or molecular asymmetry. In the snail, *Limnaea peragra*, the former mechanism appears to operate; direction of shell coiling is influenced by maternal genotype[39] perhaps relating to the asymmetrical arrangement of cells surrounding the oocyte.[40] In this situation another paradox arises. This is that if the development of bias in one generation requires maternal phenotypic bias in the previous generation genetic change alone cannot lead to the origin of bias during evolution in a bilaterally symmetrical organism. Bias could however arise as a phenotypic response which initiates a cycle leading to the transmission of the bias in the form of phenotypic information to the next and future generations. This hypothesis leads to the prediction that non-lethal experimental interference with asymmetrical maternal influences during oogenesis might result in the heritable loss of bias.

A final problem again concerns maternal influences. There is evidence that the effects of an acquired phenotypic change in the mother can be transmitted further than one generation.[41,42] An interesting example occurs in mammals where good maternal nutrition can cause high milk production and large offspring. These offspring may in turn produce more milk affecting progeny size in the second generation. It is assumed that such an effect will be diluted over generations; for this reason the phenomenon is not usually regarded as an example of extranuclear inheritance.[1] In biometrical analysis the effect is seen as a result of maternal environment and becomes partitioned into the variance due to common environment.[43] Transmission over several generations is interpreted as the inheritance of an acquired maternal environmental effect. This seems unsatisfactory since the agent of the effect is phenotypic not environmental. An alternative interpretation is that phenotypic information becomes stored in body size as a result of good nutrition and is then transmitted by a causal cycle linking body size to milk yield. This interpretation facilitates speculation that long term inheritance of acquired phenotypic effects may occur. Dilution of the effect can be interpreted as a trend in phenotypic information. Effects of this sort may also interact with cultural inheritance as when poor nutrition adversely affects the intelligence of offspring.

Acknowledgements

I thank Professor L. Van Valen for helpful critical comments on an earlier version of this manuscript.

References

(1) Jinks, J.L., *Extrachromosomal inheritance*, Prentice Hall, New Jersey (1964).

(2) Shannon, C.E., and Weaver. W.. *The Mathematical Theory of Communication*, University of Illinois Press, Illinois (1949).

(3) Brillouin, L., *Science and Information Theory*, Academic Press, New York (1962).

(4) Thompson, D.W., *On Growth and Form*. Cambridge University Press, Cambridge (1917).

(5) Cohen, J., *in* Newth, D.R., and Balls, M. (Editors). *Maternal Effects in Development*. pp. 1-28, Cambridge University Press, Cambridge (1979).

(6) Schroedinger, E., *What is Life?*, Cambridge University Press, Cambridge (1944).

(7) Dover, G., *Nature, Lond.*, *229*, 111 (1982).

(8) Gorczynski, R.M., and Steele, E.J., *Proc. natn. Acad. Sci. USA*, *77*, 2871 (1980).

(9) Steele, E.J., *Somatic Selection and Adaptive Evolution: On the Inheritance of Acquired Characters*, Croom Helm, London (1980).

(10) Brent, L., Rayfield, L.S., Chandler, P., Fierz. W., Medawar, P. B.. and Simpson, E., *Nature, Lond., 290*, 508 (1981).

(11) Sonneborn, T.M., *Proc. R. Soc.. B176*, 347 (1970).

(12) Landman, O.E., and Halle, S., *J. mol. Biol., 7*, 721 (1963).

(13) Curtis, A.S.G., *Archs. Biol., 76,* 523 (1965).

(14) Novick, A., and Weiner, M., *Proc. natn. Acad. Sci. USA*, *43,* 553 (1957).

(15) Best, J.B.. *Int. Rev. Cytol., 9,* 129 (1960).

(16) Szilard, L., *Proc. natn. Acad. Sci. USA*, *46*, 277 (1960).

(17) Beale, G.H., Proc. Roy. Soc., *B148*, 308 (1958).

(18) Durrant, A., *Nature, Lond., 181*, 928 (1958).

(19) Perkins, J.M., Eglington, E.G., and Jinks, J.L., *Heredity*, *27*, 441 (1971).

(20) Pattison, I.H., and Jones, K.M., *Nature, Lond., 218*, 102 (1968).

(21) Lansing, A., *Ann. N.Y. Acad. Sci., 57*, 455 (1954).

(22) Hinshelwood, C., *The Chemical Kinetics of the Bacterial Cell*, Clarendon Press, Oxford (1947).

(23) Pollock, M.R., *Symp. Soc. Gen. Microbiol., 3*, 150 (1953).

(24) Waddington, C.H., *Evolution, 7*, 118 (1953).

(25) Davidson, E.H., *Gene Activity in Early Development*, Academic Press, New York (1976).

(26) Briggs, R.W., Green, E.U., and King, T.J., *J. exp. Zool.*, *116*, 455 (1951).

(27) Conklin, E.G., *ibid.*, *60*, 1 (1931).

(28) Gurdon, J.B., *The Control of Gene Expression in Animal Development*, Clarendon Press, Oxford (1974).

(29) Britten, R.J., and Davidson, E.H., *Science, 165*, 349 (1969).

(30) Thoday, J.M., *Heredity, 28*, 263 (1972).

(31) Michaelis, P., *Adv. Genet., 6*, 287 (1954).

(32) Danielli, J.F., *Proc. R. Soc., B148*, 321 (1958).

(33) Moore, J.A., *Adv. Genet., 7*, 139 (1955).

(34) Gurdon, J.B., *Heredity, 16*, 305 (1961).

(35) Lewontin, R.C., *The Genetic Basis of Evolutionary Change*, Columbia University Press, New York (1974).

(36) Ehrman, L., Thompson, J.N., Perelle, I., and Hisey, B.N., *Genet. Res., 32*, 231 (1978).

(37) Morgan, M.J., and Corballis, M.C., *Behav. Brain Sci., 2*, 270 (1978).

(38) Wolpert, L., *J. theor. Biol., 25*, 1 (1969).

(39) Sturtevant, A.H., *Science, 58*, 269 (1923).

(40) Ubbels, G.A.. Bezem, J.J., and Raven, C.P., *J. Embryol. exp. Morph., 21*, 445 (1969).

(41) Denenberg, V.H., and Rosenberg, K.M., *Nature, Lond., 216*, 549 (1967).

(42) Wehmer, F., Porter. R.H., and Scales, B., *ibid.*, *227*, 622 (1970).

(43) Falconer, D.S., *Introduction to Quantitive Genetics*, Longman, New York (1981).