that CD2 activation epitopes are essential in T-cell activation, but the physiological ligand for $T11_3$ remains undefined.

The antibodies whose binding is affected by CD2 mutations around residue Lys 48 are strongly mitogenic in combination with either anti-$T11_3$/1Mono2A6 or antibody 9.1 (S. Denning *et al.*; S. Yang *et al.*, in ref. 9). Although these mutations are generally associated with diminished erythrocyte binding in Peterson and Seed's studies[2], however, only some but not all the antibodies block rosetting[9]. Thus, residue 48 of CD2 defines a region of the molecule that is essential for pairwise antibody activation but may be peripherally involved with LFA-3 recognition. In contrast, the antibodies whose binding is affected by mutations around CD2 residue Gly 95 are generally not mitogenic with anti-$T11_3$ although they do uniformly block erythrocyte rosettes (D. Olive *et al.*, in ref. 9). Most interestingly, each of this group of antibodies is mitogenic with the 9.1 anti-CD2 antibody only in the presence of a poorly mitogenic anti-CD3 antibody, which binds to invariant chains of the TCR. This suggests that Gly 95 defines a region of CD2 essential for LFA-3 recognition, and which may also be involved in interactions between CD2 and the TCR complex.

Accumulating evidence suggests CD2:TCR interactions are essential in antigenic stimulation of $CD2^+CD3^+$ T cells. The combination of a poorly mitogenic anti-CD3 antibody and a single anti-CD2 antibody provides synergistic proliferative stimuli to T cells, suggesting that each moiety is providing a minimal signal but that the combination is fully activating[11]. Physical proximity of CD2 and TCR could contribute to this synergy, because crosslinking of TCR and CD2/T11 molecules by beads carrying both anti-T3 and non-mitogenic anti-$T11_1$ antibodies markedly potentiates T-cell activation (P. Anderson *et al.*, personal communication). Furthermore, stimulation of T cells by anti-$T11_2$ plus $T11_3$ causes potent activation of cellular kinases with phosphorylation of CD3 chains[12], suggesting that CD2 and TCR function are linked. In fact, in TCR-negative mutants of a human T-cell lymphoblastoid cell line, CD2 surface molecules cannot express the $T11_3$ activation epitope or generate intracellular calcium mobilization after anti-$T11_2$ plus $T11_3$ stimulation[13], suggesting that CD2 function depends on proximity of the TCR.

In all likelihood, then, LFA-3 adhesion to CD2/T11 and TCR recognition of antigen/MHC are synergistic rather than additive in stimulating T-cell activation during cell–cell contacts (see Fig. 2). LFA-3 binding to CD2 could cause activation (signal 1) if additional stimuli are provided to CD2 activation epitopes (such as $T11_3$). Complex formation between CD2 and the T-cell antigen receptor could cause synergistic activation signals (signal 2). Preliminary results[13] suggest that crosslinking LFA-3 on the accessory cell induces secretion of interleukin-1 (signal 3), although the data do not yet reveal whether transmembrane or lipid-anchored forms of LFA-3 mediate this signal. □

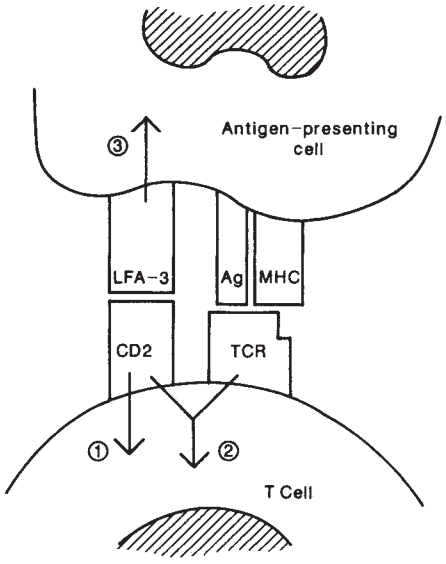


Fig. 2 Proposed intermolecular interactions during cell–cell contact between a T lymphocyte and an antigen-presenting or target cell. The TCR recognizes antigen in association with major histocompatibility complex products (Ag + MHC), whereas CD2 molecules interact with LFA-3. Potential activating signals resulting from these interactions include: (1) CD2 stimulation from LFA-3 binding in combination with a second signal delivered to the $T11_3$ epitope; (2) activation signals resulting from functional interactions of CD2 and the TCR; and (3) induction of lymphokine release in the accessory cell from LFA-3 perturbation. See text for details.

1. Seed, B. *Nature* **329**, 840–842 (1987).
2. Peterson, A. & Seed, B. *Nature* **329**, 842–846 (1987).
3. Dustin, M.L. *et al. Nature* **329**, 846–848 (1987).
4. Cross, G.A. *Cell* **48**, 179–181 (1987).
5. Wallner, B.P. *et al. J. exp. Med.* **166**, 923–932 (1987).
6. Williams, A.F. *Immun. Today* **8**, 298-303 (1987).
7. Cunningham, B.A. *et al. Science* **236**, 799–806 (1987).
8. Meuer, S.C. *et al. Cell* **36**, 897–906 (1984).
9. McMichael, A.J. (ed.) *Leukocyte Typing III* (Oxford University Press, 1987).
10. Hünig, T. *et al. Nature* **326**, 298–300 (1987).
11. Yang, S., Chevaib, S. & Dupont, B. *J. Immun.* **137**, 1097-1103 (1987).
12. Breitmeyer, J.B. *et al. J. Immun.* **139**, 2899–2905 (1987).
13. Le, P. *et al. Fdn Proc. Abstr.* **46**, 447 (1987).

James B. Breitmeyer is in the Division of Tumor Immunology at the Dana-Farber Cancer Institute, and at the Harvard Medical School, Boston, Massachusetts 02115, USA.

Natural selection

When learning guides evolution

John Maynard Smith

A PERENNIAL problem for evolutionary biologists is how natural selection can give rise to a complex structure that is of value to the organism when fully formed, but useless until it is complete. The orthodox answer, and I think often the correct one, is that it doesn't, and that complex structures have passed through a number of stages, each a little better than the last. For example, even random sequences of amino acids can have some, rather non-specific, catalytic activity. The vertebrate eye could not arise in a single step, but a single light-sensitive cell is better than nothing, a light-sensitive cell with a layer of pigment to one side is better still, and so on. That is to say, evolution is a hill-climbing process. In a recent paper, G.E. Hinton and S.J. Nowlan (*Complex Systems* **1**, 495; 1987) suggest how a combination of evolution and learning may make possible the evolution of a structure that is of value only when perfect.

An idea that has always had attractions is that adaptations acquired during an individual's lifetime, by learning or in other ways, are passed on to its offspring. For Lamarck, such inheritance of acquired characters was a main cause of evolution. For Darwin, natural selection was primary, but he also ascribed a role to "the effects of use and disuse". Weismann rejected the whole idea, essentially because he could not think of a mechanism whereby the structures acquired by an individual — for example, the blacksmith's muscles — could be translated into information in the gametes. With the development of modern genetics, and in particular of molecular biology, we have come to reject the idea that individual adaptation can alter the information in the gametes.

Even if we accept Weismann's view completely, however, it is still possible for individual learning to facilitate evolution. If individuals vary genetically in their capacity to learn, or to adapt developmentally, then those most able to adapt will leave most descendants, and the genes responsible will increase in frequency. In a fixed environment, when the best thing to learn remains constant, this can lead to the genetic determination of a character that, in earlier generations, had to be acquired afresh each generation. The idea goes back to J.M. Baldwin (*Am. Nat.* **30**, 441; 1896), C. Lloyd Morgan (*Science* **4**, 733; 1896) and C.H. Waddington (*Nature* **150**, 563; 1942). It has not always been well received by biologists, partly because they have suspected it of being lamarckist (a suspicion that Waddington was curiously reluctant to allay), and partly because it was not obvious that it would work.

What Hinton and Nowlan have done is

to answer these objections. They consider the following simple model, of whose biological unreality they are well aware. Imagine an organism with a neural net in which 20 connections must be correctly set ('on' and 'off') if its fitness is to be increased: if even one connection is wrong, it is no better than if all were wrong. This is the worst type of fitness surface, as there is no slope leading to the summit. There are 20 gene loci, each with three alleles, 0, 1 and ?. The first two specify on and off, and the third that the connection can be varied. During learning, an individual tries out a succession of settings for these variable connections. If, by chance, it tries out a correct set, and its genetically specified connections are also correct, it is rewarded, and does not alter its settings again. An individual makes 1,000 trials in its life. Its darwinian fitness is increased by a factor of $1+19n/1{,}000$, where n is the number of trials after it has learnt the correct settings. Thus, an individual that is born with the correct settings genetically fixed has a fitness 20 times that of one that never learns.

Hinton and Nowlan simulated a population of 1,000, with initial gene frequencies of 0.5 of ? and 0.25 of 0 and 1 at each locus. Because on average 10 loci were fixed, about one individual in 1,000 would have all the fixed settings correct. Also, with 10 variable settings, it would have a reasonable chance of learning the correct settings in 1,000 trials. Individuals were chosen as parents with probabilities proportional to their fitnesses. Reproduction was sexual. The response to selection was rather slow for the first 10 generations, because most individuals never learnt, but the response then accelerated, and after 20 generations the frequency of correct alleles was high, and learning was rapid.

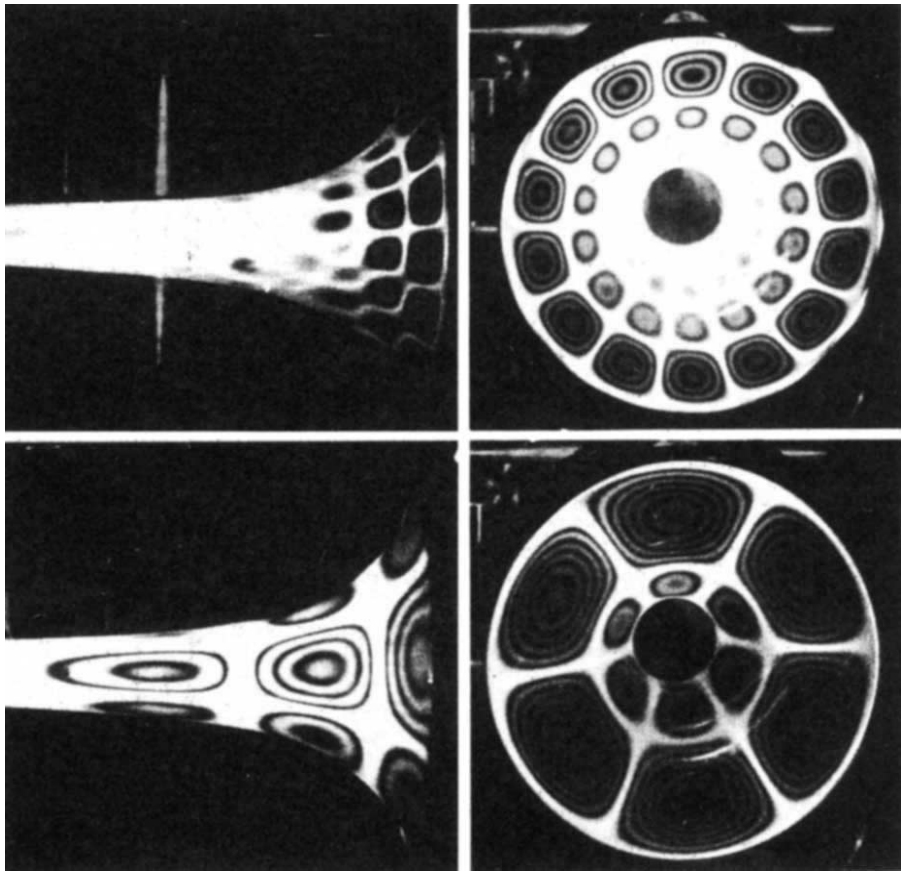
To what extent has learning accelerated evolution in this model? The absence of learning would be represented by the case in which only 0 and 1 alleles were present. There are then approximately 10^6 genotypes, of which one has a fitness of 20 and all the rest of 1. In a sexual population of 1,000, with initial allele frequencies of 0.5, a fit individual would arise about once in 1,000 generations (I ignore the fact that some wrong alleles would, in time, be fixed by genetic drift). Mating would disrupt the optimum genotype, however, and its offspring would have lost the adaptation. In effect, a sexual population would never evolve the correct settings.

What of an asexual population? An asexual population of 1,000 would be unlikely to include an optimal individual, and, unless one assumes an unreasonably high mutation rate, would never give rise to one. But a population of many millions would include optimal individuals that would breed true, and the correct settings would soon be established by selection.

Two comments are worth making. First, an asexual population, without learning, would try out more than 10^6 individuals before solving the problem, compared with 20,000 for the simulated sexual population with learning. Second, in the absence of learning, a large asexual population can evolve the adaptation, whereas a sexual one cannot (or does so excessively slowly). This illustrates the general fact that, when there are epistatic fitness interactions, sexual reproduction can actually slow down evolutionary progress, by breaking up co-adapted groups of genes as soon as they arise. (Epistasis arises in the present example because if, for example, A and B are correct alleles, and a and b incorrect ones, then A is fitter than a in the presence of B, but not in the presence of b.) Because sexual reproduction is almost universal, I wonder whether epistatic interactions can be as widespread as is sometimes thought.

Hinton and Nowlan show there are contexts in which learning (or developmental flexibility) speeds up evolution. It does so by altering the search space in which evolution operates, surrounding the optimum by a slope which natural selection can climb. To use their analogy, finding the optimal neural net in the absence of learning is like searching for a needle in a haystack. With learning, it is like searching for the needle when someone tells you when you are getting close. □

John Maynard Smith is Professor of Biology at the University of Sussex, Falmer, Brighton, Sussex BN1 9QG, UK.



THE shining brass of a trombone might look good, but does it have any effect on the sound produced? If the walls merely define the boundary of the vibrating column of air, one might just as well make trombones from plastic. On the other hand some musicians swear blind by their own favourite alloy. The figure shows the measured vibrations of a trombone bell played at 1,000 Hz (upper) and 630 Hz (lower). (Side-on views, left; end-on views right.) The holographs were recorded at the National Physical Laboratory, near London, as part of a study, by instrument designer Richard Smith, into the relationship between bell shape, material and sound. The contours reveal a distortion of the bell by a wavelength of laser light, about 0.5μm. The tests show that thinner bells vibrate more, and certain harmonics of some of the notes produced were up to 2 decibels stronger. Material effects were only apparent in thin-walled instruments. Blindfolded professional trombonists, however, were unable to hear the difference, and also were unable to distinguish the instruments in performance if they were adjusted for weight and balance. An electroformed pure-copper bell introduced in the blindfold tests went unnoticed, but mysteriously took on wonderful properties when the blindfolds were removed, copper being a 'superior' material. (Courtesy of Richard Smith, 110 The Vale, London N14 6AY, UK.) □