Evolution and Climate Variability

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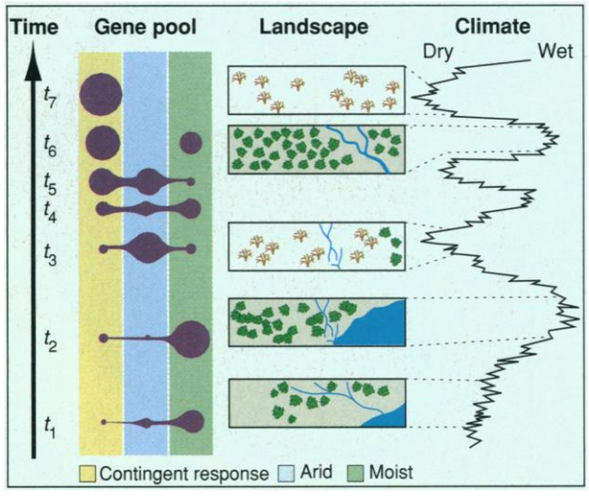
Variations in organisms are preserved and accrue if there is a consistent bias in selection over many generations. This idea of long-term directional selection has been embraced to explain major adaptive change (*1*). It is widely thought that important adaptive shifts in hominids corresponded with directional environmental change. This view, which echoes the savanna scenario of hominid evolution (*2*), has strongly been supported by paleontologists and paleoclimatologists over the past decade (*3*).

According to deMenocal (*4*), periodic increases in aridity occurred during the late Pliocene and early Pleistocene, favoring the evolution of arid-adapted taxa, including hominids. The late Cenozoic deep-sea oxygen-isotope ($\delta^{18}O$) record shows what is considered to be marked global cooling and drying in Africa; species turnover in bovids, rodents, and hominids is said to correlate with stepwise expressions of the climatic trend (*5*). The origin of the hominids, bipedality, stone toolmaking, and brain size increase have all been related to cooling, aridification, and savanna expansion (*3–6*).

There is, however, a more prominent signal than the aridity trend: an increase in the range of climatic variation over time. Amplitude variation in $\delta^{18}O$, bottom-water temperature, sea surface temperature, and dust records increased over the past 5 million years by a factor of 2 or 3 (*4*, *7*). This variation was mirrored by fluctuation in vegetation and moisture, particularly over the past 1 million years. Pleistocene records from Africa, Europe, and Asia indicate repeated shifts in regional hydrology and vegetation (*8*). The widest extremes were expressed over intervals of 10 to 100 thousand years and differed qualitatively from seasonal variations. Subsequent remodeling of landscapes likely had strong effects on water and food sources, population densities, biotic competition, and thus natural selection.

Hardly just noise, long-term fluctuation was a signal of potentially major evolutionary consequence. I have proposed the term "variability selection" (*9*) to describe the effects of repeated, dramatic shifting in Darwinian selection over time. This inconsistency over many generations may have had an important impact on hominid evolution.

Variability selection requires a long sequence of large-scale habitat oscillation such that individuals of a lineage living at different times experience different adaptive conditions. Over a span of recurrent extremes, some gene combinations and complex behaviors may be favored that enable resilient and novel responses to new conditions (see figure) unlike those resulting from any single generation of Darwinian selection. By positing that complex specializations may arise as a result of temporal disparities in fitness, the concept of variability selection challenges the common idea that major adaptive change requires long-term consistency in relative fitness.



Variability selection in a Mendelian population. Environmental oscillation (right) is reflected (Landscape) by fluctuation in vegetation (green) and surface water (blue). At t_1, a lake is fed by a river system in open woodland. After wet and dry extremes, surface water disappears (t_7). The gene pool (and associated phenotypes) is divided into (i) features favored in moist, highly vegetated settings; (ii) features that yield higher fitness in dry, open habitats; and (iii) contingent responses, which are favored under novel circumstances and depend on environmental input. The size of the shapes under "Gene pool" depicts relative fitness in each specific interval of time. The dominance of genotypes that confer contingent responses over habitat-specific adaptations (t_5 to t_7) cannot be extrapolated from the short-term fitness results of earlier intervals. In variability selection, complex mechanisms of mediating environmental information and novel response may evolve.

Although it is hard to discern Mendelian populations in the fossil record, four lines of evidence emerge for hominids. First, adaptive flexibility is correlated with wider environmental oscillation. As global climate variability rose between 3 and 5 million years ago, a form of bipedality emerged that could accommodate terrestrial and arboreal settings. Increase in relative brain size, technological innovation, manipulation of symbols, and geographic diversity in behavior are all apparent in the late Pleistocene. The emergence of these features, suggestive of a novel responsiveness to environments, corresponded with the largest recorded oscillations of the late Cenozoic (*7*, *8*).

Second, stratified sites such as Olduvai Beds I and II and Combe Grenal record long periods of environmental change and the continuous presence of hominids (*10*). Although many organisms followed favored habitats over time, certain hominid populations coped with large landscape changes within regions.

Third, there was turnover in other mammals. Five previously dominant herbivores in southern Kenya became extinct 800 to 400 thousand years ago and had traits that indicate a reliance on low-quality forage (*11*). When environmental fluctuation became extreme, especially after 600 thousand years ago, they were survived by closely related taxa that could switch diet in different settings, had smaller bodies and dental morphologies (indicating less specialized grazing), and may have had wider habitat ranges. Thus, in these groups, habitat or dietary specialists were replaced by lineages having flexible response.

Fourth, this process of sorting species within a clade seems to have occurred within the hominids. Although early Pleistocene *Paranthropus* appears to have been omnivorous, its massive craniofacial and dental apparatus indicates heavy mastication and thus specific dietary requirements (*12*). Later in the Pleistocene, Neanderthals exhibited a geographic range and anatomical traits (such as short distal limb segments) that imply adaptation to cold environments (*13*). In both cases, hominids with a more restricted geographic range became extinct, whereas those with greater mobility and behavioral diversity (early *Homo erectus* and modern *H. sapiens*) persisted.

During hominid evolution, the episodic revamping of climate, vegetation, and vital resources was a key environmental signal. The inconsistency of Darwinian optima was likely its own unique selective process and may have been responsible for the overall pattern of hominid evolution and key adaptive features in the genus *Homo*.

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References

1. N. Eldredge, *Macroevolutionary Dynamics* (McGraw-Hill, New York, 1989), p. 34; J. A. Endler, *Natural Selection in the Wild* (Princeton Univ. Press, Princeton, NJ, 1986).
2. R. G. Klein, *The Human Career: Human Biological and Cultural Origins* (Univ. of Chicago Press, Chicago, 1989), pp. 98–99.
3. E. S. Vrba, in *Evolutionary History of the "Robust" Australopithecines*, F. E. Grine, Ed. (de Gruyter, New York, 1988), pp. 405–426; M. L. Prentice and G. H. Denton, *ibid.*, pp. 383–403; E. S. Vrba, G. H. Denton, T. C. Partridge, L. H. Burckle, Eds., *Paleoclimate and Evolution* (Yale Univ. Press, New Haven, CT, 1995), pp. 3, 19, 285, 342, 351, 362.
4. P. B. deMenocal, *Science* **270**, 53 (1995).
5. E. S. Vrba, G. H. Denton, M. L. Prentice, *Ossa* **14**, 127 (1989).
6. S. Stanley, *Paleobiology* **18**, 237 (1992).
7. W. F. Ruddiman *et al.*, *Proceedings of the Ocean Drilling Program, Scientific Results 108* (1989), p. 463; R. Tiedemann, M. Sarnthein, N. J. Shackleton, *Paleoceanography* **9**, 619 (1994).
8. G. Kukla, *Palaeogeogr. Palaeoclimatol. Palaeoecol.* **72**, 1 (1989); R. Potts, *J. Hum. Evol.* **27**, 7 (1994); A. M. Van der Weil and T. A. Wijmstra, *Rev. Palaeobot. Palynol.* **52**, 73 (1987); M. Rossignol-Strick, *Nature* **304**, 46 (1983); P. deMenocal, W. F. Ruddiman, E. M. Pokras, *Paleoceanography* **8**, 229 (1993).
9. R. Potts, *Humanity's Descent: The Consequences of Ecological Instability* (Morrow, New York, 1996).
10. R. L. Hay, *Geology of the Olduvai Gorge* (Univ. of California Press, Berkeley, 1976); P. Mellars, *The Neanderthal Legacy* (Princeton Univ. Press, Princeton, NJ, 1996).
11. R. Potts and A. Deino, *Quat. Res.* **43**, 106 (1995).
12. A. Sillen, *J. Hum. Evol.* **23**, 495 (1992); F. E. Grine, Ed., *Evolutionary History of the "Robust" Australopithecines* (de Gruyter, New York, 1988), pp. 3–42, 55–83, and 193–198.
13. E. Trinkaus, in *Aspects of Human Evolution*, C. B. Stringer, Ed. (Taylor & Francis, London, 1981), pp. 187–224.

A New Receptor for Growth Hormone–Release Peptide

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In 1984, a synthetic hexapeptide was developed that causes release of growth hormone from the pituitary gland. But even then there were hints that this synthetic peptide (called GHRP, for growth hormone release peptide) and the natural growth hormone–releasing hormone acted at distinct receptors in the pituitary, suggesting that GHRP was mimicking a second "endogenous factor or . . . hormone that regulates growth hormone release" (*1*, p. 1542). Now in this issue of *Science*, a group of researchers from Merck reports the cloning of the receptor for these synthetic growth hormone secretagogues (*2*), clinching the existence of a second route for growth hormone regulation, and opening the door for identification of the endogenous ligand for this receptor.

Until recently the typical path leading to the development of a drug has been to identify the active compound and then to make analogs that recognize the target (usually a receptor or an enzyme). But Howard *et al.* (*2*) have followed a different route: They identified a potential lead drug before the identification of either the endogenous active compound or the receptor. The scientific history that led to this development is a fascinating story of independent accomplishment by individuals whose efforts may now be resulting in a valuable new class of drug.

It was recognized for years that opiates can cause release of growth hormone; indeed, certain peptide analogs of the opiate Met-enkephalin actually lack opiate activity but still cause release of growth hormone (*3*). The best of these early compounds GHRP-6 (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) was interesting, because it had the biological activity of a hypothalamic growth hormone–releasing hormone (*1*). However, it contains two uncoded D–amino acid residues and so is clearly not naturally present in mammals.

At about the same time, a natural 44–amino acid protein from the hypothalamus was identified that causes release of pituitary growth hormone (GHRH) (*4*). Defying a number of predictions, GHRP-6 did not compete with GHRH for its receptor (*5*). Likewise, a proposed mechanism of action in which GHRP-6 caused growth hormone release by inhibiting the binding of somatostatin (which inhibits growth hormone release) to its receptor was excluded. In fact, GHRP-6 could synergize with GHRH to release growth hormone in animals and humans (*5*, *6*).

GHRP-6 and its chemical descendants were licensed to a series of drug companies whose researchers prepared peptidic analogs in the hope of identifying some that might promote growth hormone release in humans or be useful for veterinary purposes. And GHRP-6 and its analogs did show potent growth hormone–releasing activity by intravenous, subcutaneous, intranasal, and oral routes in humans and topically in mice (*7*–*9*).

In 1990, recombinant human growth hormone (rhGH) was shown to increase the quality of life for otherwise healthy men aged 61 to 81 with low plasma concentrations of insulin-like growth factor–1 (IGF-1) of 350 units per liter (the "youthful" range is 500 to 1500 units per liter) (*10*). In the experimental group, who received rhGH three times weekly for 6 months, the IGF-1 value moved into the youthful range, accompanied by an increase in lean body mass, a decrease in adipose tissue mass, and an increase in average lumbar vertebral bone density. Skin thickness also increased. But thrice weekly self-administration of rhGH would be expensive as a routine treatment, and aging patients would likely have difficulty with compliance. Clearly, a drug that would cause release of the individual's own growth hormone would be preferable, especially if a version with oral activity were available. Physicians treating short-statured children, as well as veterinarians, would find such compounds useful. Another advantage would be that the GHRP-like compounds increase growth hormone secretion in the normal pulsatile pattern and so, in contrast to rhGH administration, might be less likely to have any adverse clinical effects in older subjects.

The Merck group has now identified compounds that may fulfill the criteria of useful agents and has used them to clone the receptor for this class of compounds (*2*, *11*–*13*). Their findings demonstrate the existence of an endogenous system, distinct from GHRH and somatostatin, that participates in the regulation of growth hormone release. This "reverse pharmacology" then gives us access to the receptor, as well as (presumably) agonists for it, even before we know the endogenous ligand or the precise physiological role of the receptor. Identification of the receptor unequivocally establishes a novel target of action for this drug class.

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References

1. C. Y. Bowers, F. Momany, G. A. Reynolds, A. Hong, *Endocrinology* **114**, 1537 (1984).
2. A. D. Howard *et al.*, *Science* **273**, 974 (1996).
3. C. Y. Bowers *et al.*, *Endocrinology* **108**, 1071 (1980).
4. R. Guillemin *et al.*, *Science* **218**, 585 (1982).
5. C. Y. Bowers, A. O. Sartor, G. A. Reynolds, T. M. Badger, *Endocrinology* **128**, 2027 (1991).
6. C. Y. Bowers *et al.*, *J. Clin. Endocrinol. Metab.* **70**, 975 (1990).
7. J. Bellone *et al.*, *Eur. J. Endocrinol.* **133**, 425 (1995).
8. J. Frenkel, A. Silbergeld, R. Deghenghi, Z. Laron, *J. Pediatr. Endocrinol.* **8**, 43 (1995).
9. D. Fleisher *et al.*, *Life Sci.* **57**, 1293 (1995).
10. D. Rudman *et al.*, *N. Engl. J. Med.* **323**, 1 (1990).
11. A. A. Patchett *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 7001 (1995).
12. R. G. Smith, *10th International Congress of Endocrinology*, 12–15 June 1996, San Francisco, CA (abstr.), p. 26.
13. C. Y. Bowers, *J. Clin. Endocrinol. Metab.* **79**, 940 (1994).