

of this tree are dispersed almost exclusively by the spider monkey (*Ateles paniscus*; Fig. 1). Three other primate species feed upon the tree's seeds in the study area, but only spider monkeys ingest them intact and act as effective dispersal agents. The monkeys can travel 1 kilometre in a few minutes and have a gut passage time of about 4 hours. So the seeds can be dispersed some distance from the parent plant, ensuring that the genetic structure of the population of *I. ingoides* is well mixed.

The research concentrated on the genetic variability of *I. ingoides* populations, comparing areas where spider monkeys were present with those where they had become locally extinct through bushmeat hunting. After analysing 14 enzyme systems in leaf extracts, the authors found that there was less genetic variation in the seedling populations around parent trees when the monkeys were absent than when they were present. Without the monkeys the seeds simply fall to

the ground around their parents. In other words, the monkeys are responsible for maintaining a thorough genetic mix in the population, and in their absence a series of genetically more uniform patches develops.

In general, trees in the tropical rainforest have high levels of genetic diversity. They are usually out-breeding and have efficient gene flow because of their specialized pollination and seed-dispersal mechanisms. Fragmentation of the forest, whether by physical processes (such as clearance) or by interruption to gene flow (as in the case of vector loss), can lead to the local accumulation of potentially detrimental mutations and an overall loss of fitness. As has so often proved to be the case in ecological studies, when one link is removed from a network, the whole system can start to unravel. ■

Peter D. Moore is in the Division of Life Sciences, King's College, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NN, UK.  
e-mail: peter.moore@kcl.ac.uk

## Biochemistry

# Single-handed cooperation

Jay S. Siegel

Our bodies use only 'left-handed' amino acids and 'right-handed' sugars. Hints are now emerging on how this handedness evolved and how cooperativity among like-handed molecular components came about.

The sequencing of the human genome provides exciting possibilities to explain the complexities of life. But some more basic questions remain unanswered — such as why the double-helix structure of DNA spirals in a clockwise (right-handed) direction, rather than a left-handed one. On page 797 of this issue<sup>1</sup>, Ghadiri *et al.* use a peptide system to demonstrate how 'homochirality', or single-handedness, may have evolved in biological molecules.

Nucleic acids, like nearly all biological molecules, exhibit 'handedness', and only one of the two forms is used in a particular biological process. This gives rise to homochirality, where each molecule is identical. Among sugars, ribose and deoxyribose are not identical; nonetheless, the form of ribose in RNA and the form of deoxyribose in DNA share a common right-handed orientation of their principal functional groups. This common stereochemistry — the three-dimensional shape of the molecule — evokes another concept of homochirality, which relates members of a family of compounds.

The natural amino acids share a common stereochemistry, as they are all left-handed (L-amino acids). This raises the question of whether homochirality within a family of biological molecules is the result of a stereochemical cooperativity (diastereo-

selectivity) among the members within a biopolymer. Indeed, our enzymes and nucleic acids are composed of predominantly L-amino acids and D-sugars — we are unable to use the opposite-handed biopolymers. Why not? Attempts to answer this question by mimicking the creation of a homochiral environment in the laboratory have been unsuccessful until now.

This difference in functional chiral form had tragic consequences in the 1960s when pregnant women were given a sedative (Thalidomide) that was a mixture of the right- and left-handed forms of the drug; one of the two forms, or enantiomers, gave rise to birth defects. That two enantiomers can have such different functions shows that stereochemistry controls whether, and how, molecules recognize one another and 'shake hands'.

The origin of one-handedness in biological molecules is not yet clear<sup>2</sup>. Several explanations have been put forward to explain how homochirality came about, but all are speculative — it is not even known yet whether it arose by chance or by some other means<sup>3,4</sup>.

Synthetic polymers are simpler than biological systems and provide a model for understanding the origin of homochirality in biomolecules. One proposal stems from observations that polymers made from



## 100 YEARS AGO

**Sensational Newspaper Reports as to Physiological Action of Common Salt.** In the interest of the dignity of scientific research I venture to hope you will print the following statement. Some American papers have recently published sensational and absurd reports of physiological theories and experiments whose authorship they attributed to me. These reports, which in America nobody takes seriously, were reprinted and discussed in European papers. I hardly need to state that I am in no way responsible for the journalistic idiosyncrasies of newspaper reporters and that for the publication of my experiments or views I choose scientific journals and not the daily Press. Jacques Loeb  
From *Nature* 14 February 1901.

## 50 YEARS AGO

A recent address on "Freedom in Science" broadcast by Prof. C. A. Coulson made even clearer the need for ensuring that our instruments of government make proper provision for such freedom. Prof. Coulson observed that, since patience, humility, tolerance, fairmindedness, integrity, cooperation and trust are the hallmarks of the scientific tradition, he has been forced to the conclusion that this tradition is ultimately based on, and derives its final sanction from, moral and ethical considerations which lie outside the field of what is popularly called science. A. N. Whitehead maintained that the inner conviction that the world is rational, and the confidence in one another that enables us to dispense with the verification of other people's claims, is a legacy coming to us from "the medieval insistence on the rationality of God". Prof. Coulson accordingly suggests that in a time of crisis like the present, which is marked by the breakdown of personal conviction among ordinary people, it is highly important that... men of science are the custodians of many of the most precious values of our civilization. From this aspect, Prof. Coulson agrees with Prof. Polanyi's view that the suppositions underlying our belief in science "co-extend with the entire spiritual foundations of man, and go to the very root of his social existence". But he discusses a possible danger to the freedom of science which might well arise from intoxication with power and an unmeasured faith in organization. This will have to be guarded against when the Science Centre in London now under consideration is established.  
From *Nature* 17 February 1951.

building blocks of random handedness will contain mixtures of right- and left-handed blocks so complex that no two polymers will have identical stereochemistry. All the polymers will be chiral, but if one exists, it is unlikely that its mirror image will too<sup>5</sup>. For small polymers consisting of only a few building blocks, the number of possible combinations of right- and left-handed blocks is small, and the mirror images are easily formed. However, for a polymer comprising 20 building blocks there are almost a million possibilities, and an enormous number of blocks would be required to build all the possible mirror images. Biological molecules often have over 100 building blocks, pushing the limits of available materials and making it extremely unlikely that a molecule and its mirror image can be prepared in the same batch. If the sample of polymers contained some that were self-replicating, it is reasonable that the most efficient one will emerge, and only this homochiral polymer will exist<sup>6</sup>.

In complex organisms and living systems,

homochirality manifests itself in families of related biological molecules, such as the naturally occurring L-amino acids in a protein. The presumption here is that there is cooperativity among these biomolecules in their biopolymers or underlying structure. The polymer example above alludes to an optimum self-replicating polymer. Can we form a general rule that homochirality leads to optimal function? With regard to self-replication, this question can be addressed by stereochemical analysis and reaction engineering. However, engineering the parameters of biochemical processes to obtain appropriate stereoselectivity — choosing of the preferred mirror image — has not been trivial. Poor reaction selectivity and inhibition of replication have plagued researchers who would like to mimic life through protobiology<sup>7</sup>.

Ghadiri *et al.*<sup>1</sup> find a stereoselective reaction, between two chiral peptides, that uses the product of their coupling to replicate — a process known as ‘autocatalysis’. Their results indicate that this self-replicating

Daedalus

David Jones

David Jones, author of the Daedalus column, is indisposed.

system could perpetuate homochirality, because a left-handed template is competent to bring together only those fragments that are also left-handed. The authors also show that, even if only one out of 15 building blocks has opposite handedness, autocatalysis is significantly diminished. Such a result establishes that homochiral peptides are most efficient at autocatalysis.

The authors also found that even though a single ‘mutation’ with regard to handedness could hamper autocatalysis, the same mutant template was reasonably effective at catalysing the combination of two pure left-handed fragments. The combination of these results supports the idea that a polymer evolution experiment would ultimately result in homochirality of biological molecules. Furthermore, these results support a general principle that similarity in building blocks leads to higher-order structure, like the spiral shape of a ram’s horn or a crystal-lattice structure<sup>8,9</sup>.

Given the fundamental nature and pervasive occurrence of chirality in biological and non-biological macromolecules, it is reasonable to postulate that homochirality existed long before the genetic information of life was encoded. Once in place, this sense of chirality perpetuated throughout early life systems and has become a part of complex biochemical processes such as translation and transcription. So the linear sequence of information on the genome is passed along owing to the three-dimensional structure of the DNA double helix, and must now include the coding for homochirality that we see in amino acids. We now have a model system that may bring us closer to understanding why we see cooperativity among homochiral biological molecules today.

Jay S. Siegel is in the Department of Chemistry, University of California San Diego, La Jolla, California 92093-0358, USA.  
e-mail: [jssiegel@ucsd.edu](mailto:jssiegel@ucsd.edu)

1. Saghatelian, A., Yokobayashi, Y., Soltani, K. & Ghadiri, M. R. *Nature* **409**, 797–801 (2001).
2. Bonner, W. A. *Orig. Life Evol. Biosph.* **25**, 175–190 (1995).
3. Siegel, J. S. *Chirality* **10**, 24–27 (1998).
4. Berger, R., Quack, M. & Tschumper, G. S. *Helv. Chim. Acta* **83**, 1919–1950 (2000).
5. Green, M. M. & Garetz, B. A. *Tetrahedr. Lett.* **25**, 2831–2834 (1984).
6. Bolli, M., Micura, R. & Eschenmoser, A. *Chem. Biol.* **4**, 309–320 (1997).
7. Kozlov, I. A., Politis, P. K., Pitsch, S., Herdewijn, P. & Orgel, L. E. *J. Am. Chem. Soc.* **121**, 1108–1109 (1999).
8. Kuhn, H. & Waser, J. *Angew. Chem. Int. Ed. Engl.* **20**, 500–520 (1981).
9. Thompson, D. *On Growth and Form* 346 (Cambridge Univ. Press, 1961).

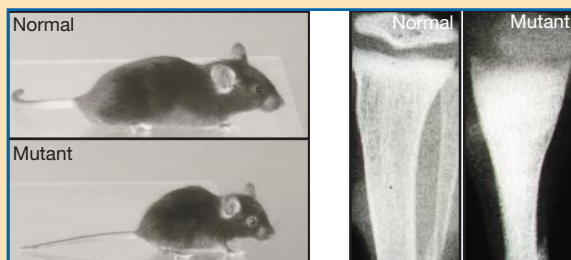
Medicine

Channel fault in osteopetrosis

Bone is a dynamic structure, constantly being formed (by cells called osteoblasts) and resorbed (by osteoclasts). The activities of these cells must be finely balanced. If resorption exceeds formation, the result is the weakened, brittle bones characteristic of osteoporosis.

In osteopetrosis, by contrast, not enough bone is resorbed: the osteoclasts malfunction, leading to dense yet fragile bones with no bone marrow. Writing in *Cell* (**104**, 205–215; 2001), Uwe Kornak, Dagmar Kasper and colleagues identify a molecule that is needed for the bone-resorbing cells to function. Their results may explain some cases of an inherited disease, infantile malignant osteopetrosis.

During bone resorption, osteoclasts attach to the bone matrix and form a specialized outer membrane, called the ruffled border, facing the bone. Bone-digesting enzymes are then transported out of the cell, across this border. The enzymes need an acidic environment to function, so the osteoclasts also pump out protons. At the same time, chloride ions are let out of



the cell to maintain the electrical balance. The protein-based channel that selectively allows the efflux of chloride ions has been elusive, but the authors suggest that it is a molecule called CIC-7.

Kornak *et al.* engineered mice with a disruption in the gene encoding CIC-7. The resulting mutant mice (one of which is pictured above, with a normal mouse) had all the characteristics of osteopetrosis, including short limbs and abnormally dense bones. The mice also failed to form bone marrow, as can be seen by comparing the two high-magnification X-ray images above. Moreover, osteoclasts isolated from the mutant mice were unable to absorb bone.

The authors tracked down the CIC-7 protein to the outer membrane and certain acidic organelles, called lysosomes, in the osteoclasts of normal mice. But there was no CIC-7 protein in these cells in the mutant mice. Although the osteoclasts from the mutant mice contained the usual proton pump in their outer membranes, they were unable to acidify the extracellular space — presumably because of the defect in CIC-7. Finally, Kornak *et al.* discovered that a patient with infantile malignant osteopetrosis has a disrupted CIC-7 gene. All in all, they make a convincing case that this chloride channel is crucial for bone resorption.

Amanda Tromans