BIOLOGICAL ASYMMETRY AND HANDEDNESS
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This is a very exciting meeting: so far as I know it is unique in its attempt to discuss left–right asymmetry, from molecules to brains. It is a brave attempt and I have no idea how it is going to go. In developmental biology left/right-handedness is rather neglected. The psychologists have been much more to the fore in thinking about this problem. Nigel Brown and I a little while ago wrote a review and sent it to what we thought was a leading journal in the field, Developmental Biology: not only did they loathe the paper but they made it quite clear that they couldn’t possibly see why anybody should want a review of this subject since no one was interested in it. I am delighted to say that I think they are entirely wrong.

I have a personal interest in this question: nobody who is left handed can not be interested in left-right asymmetry. However, my theory that people study left-right asymmetry because they are left handed is disproved by the observation that there are only two left-handed people out of 29 participants at this conference.

Perhaps the issue is the following. If life had used D-amino acids instead of L-amino acids, would we all have had our hearts on the other side? And would the laterality of the brain have been the other way around? I believe the answer is both yes and no. The ‘yes’ answer comes from Nigel Brown’s and my belief that left–right asymmetry has its origin in a handed or asymmetrical molecule. Obviously, if you change the handedness of this molecule, you will change the position of left–right asymmetrical structures in the body. The ‘no’ response is that it needn’t have been that way—the fact that the heart is on the left side is purely fortuitous. Once you have established asymmetry in development you can do what you like with it; evolution could have selected the heart to be on the left or the right. In other words, evolution could have been even handed as to where structures are put once a basic asymmetry has been established. It will be interesting to see if we can come up with a better answer during the meeting. If we can, I think we will have made quite a lot of progress.

There are a lot of problems that we have to consider, not least is why there is a handed symmetry at all. If a vertebrate has to fit the gut and other organs into the body cavity, it is perfectly reasonable to push them all to one side.
It is much less clear to me why you should do it always to the one side. What
difference does it make to an animal that the heart is always put on the left
side rather than the right side? I hope someone will provide an answer to that
particular question.

We know that asymmetry is very primitive. Joe Frankel’s ciliates’ ancestors
were probably asymmetrical too, so I would say that asymmetry in cell structure
is a very primitive character. At the multicellular level, I simply don’t know.

We want to understand the generation of left–right asymmetry. One problem
is the question of linkage: what is the relationship between one asymmetry and
another, for example handedness and arm-folding? Even in development,
handedness of asymmetrical structures is not necessarily tightly linked; that’s
a tremendous puzzle to me. If you have a mechanism for putting things on one
side and not the other, surely you do it as a unitary system, but I am not sure
that’s actually the case.
Origins of the handedness of biological molecules

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Abstract. Pasteur (1860) showed that many organic molecules form enantiomeric pairs with non-superposable mirror-image shapes, characterized by their oppositely signed optical rotation but otherwise apparently identical. Equal numbers of left-handed and right-handed molecules resulted from laboratory synthesis, whereas biosynthetic processes afforded only one of the two enantiomers, leading Pasteur to conclude that biosynthesis involves a chiral force. Fischer demonstrated (1890–1919) that functional biomolecules are composed specifically of the D-sugars and the L-amino acids and that the laboratory synthetic reactions of such molecules propagate with chiral stereoselectivity. Given a primordial enantiomer, biomolecular homochirality follows without the intervention of a chiral natural force, except prebiotically. Chiral forces known at the time were found to be even handed on a time and space average, exemplifying parity conservation (1927). The weak nuclear force, shown to violate parity (1956), was unified with electromagnetism in the electroweak force (1970). Ab initio estimations including the chiral electroweak force indicate that the L-amino acids and the D-sugars are more stable than the corresponding enantiomers. The small energy difference between these enantiomeric pairs, with Darwinian reaction kinetics in a flow reactor, account for the choice of biomolecular handedness made when life began.

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Molecular dissymmetry

Pasteur (1860) reviewed the three methods he had discovered for separating the two enantiomeric molecules of a racemic mixture. The first was manual sorting of the crystals separating out from a solution of a racemate, sodium ammonium paratartrate, into two enantiomorphous sets: small facets distinguished the crystals of one set from those of the other, relating them as non-superposable mirror-image forms. A solution of crystals of one set gave a specific optical rotation of polarized light equal in magnitude but opposite in sign to one of crystals from the enantiomorphous set, accounting for the optical inactivity of the racemate solution. At the time, the main guide to molecular form was the concept that a crystal and its constituent molecular building blocks must be
‘images of each other’ morphologically. From this, Pasteur inferred that the molecular shapes of dextrorotatory (+)-tartaric acid and laevorotatory (−)-tartaric acid have non-superposable mirror-image forms. Pasteur termed such forms ‘dissymmetric’: the equivalent term ‘chiral’ (handed) was introduced later by Kelvin.

The second method for the optical resolution of a racemate came with Pasteur’s discovery of diastereomers: these compounds contain two or more different chiral units and, unlike enantiomers, have inequivalent chemical properties. An optically active alkaloid base, such as quinine, with (+)- and (−)-tartaric acid forms salts that have different solubilities, thus allowing a ready separation of the two enantiomers from racemic paratartaric acid.

The third method had particular significance for Pasteur. He found that the mould Penicillium glaucum, grown on racemic paratartarate, preferentially uses (+)-tartrate as a carbon source, leaving the (−)-isomer, which Pasteur isolated as the ammonium salt. In his 1860 lectures Pasteur emphasized that the production of the optically active molecules then known was confined to the biosynthetic activity of living organisms, the laboratory syntheses of the time affording only optically inactive products. Accordingly, it appeared to Pasteur that in living organisms, ‘dissymmetric forces exist at the moment of the elaboration of natural organic products; forces which are absent or ineffectual in the reactions of our laboratories’. Pasteur later described some of the inconclusive experiments he had carried out in an attempt to characterize the chiral natural forces. These forces might have been magnetic, for Faraday had shown that a magnetic field induces optical activity in glass and other isotropic media, or they might have arisen from the radiation of the Sun and the rotatory motions of the Earth. Pasteur pointed out that the solar system as a whole is dissymmetrical, for it is not superposable on its mirror image.

Stereoselective chiral synthesis

Pasteur’s hopes for chirally selective synthesis in the laboratory became realizable when the purely morphological concept of molecular dissymmetry was given a three-dimensional structural basis by the tetrahedral model for the orientation of the four valencies of the carbon atom (LeBel 1874, van’t Hoff 1874). The new stereochemistry provided detailed expectations in the laboratory investigation of organic natural products. In particular, the predictions of the number and the type of stereoisomers resulting from a chain of bonded chiral carbon atoms, A-[CXY]-B, proposed by van’t Hoff (1874), were tested and subsequently used as a guide by Emil Fischer in his studies of the sugar series, 1884–1908 (Freudenberg 1966).

Fischer found, as van’t Hoff had foreseen, that there are $2^n$ stereoisomers, all optically active, if A and B are inequivalent groups, as in the aldose sugar series, HOCH$_2$-[CHOH]-CHO. The $2^n$ stereoisomers are made up of $2^n$-
chemically distinct diastereomers, each diastereomer consisting of a pair of mirror-image enantiomeric molecules, which were generally supposed to be chemically equivalent in reactions with achiral reagents.

Fischer (1894) and his colleagues evolved reaction sequences for ascent and descent of the sugar series, for a unit increase or decrease in the number \( n \) of chiral carbon atoms. In this way Fischer distinguished two enantiomeric series of sugars, the D-series related back chemically to the parental \((n = 1)\) triose, D-(+)-glyceraldehyde, and the L-series similarly related to the mirror-image triose. Subsequently, from his studies of proteins and synthetic polypeptides, Fischer characterized chemically two enantiomeric series of amino acids. He found that the homochiral biochemistry of living organisms is dominated by the D-series of sugars and the L-series of amino acids.

In his studies of the sugars, Fischer discovered that, contrary to the common understanding of the time, the synthetic reactions of an enantiomer with achiral reagents are chirally selective. In the ascent of the sugar series from the aldopentose, arabinose \((n = 3)\), to the two related hexose diastereomers, mannose and glucose \((n = 4)\), he showed that mannose is the major product and glucose the minor one, formed in such a small yield that it had remained undetected in previous researches on the sugars. Only achiral reagents, such as hydrogen cyanide, were involved in the ascent of the sugar series. The synthetic reactions of a chiral molecule with chiral reactants were even more stereoselective, and they became stereospecific in reactions mediated by enzyme catalysts.

These observations led Fischer to the view that 'the difference frequently assumed in the past to exist between the chemical activity of living cells and of chemical reagents, in regard to molecular asymmetry, is non-existent . . . once a molecule is asymmetric, its extension proceeds also in an asymmetric sense'. Starting with a single enantiomer, synthetic reactions lead inevitably to a dominant diastereomeric product favoured by the steric congruence of the reaction intermediates. The propagation of the best stereochemical fit in a synthetic reaction, Fischer's 'key and lock' hypothesis, offered 'a simple solution to the enigma of natural asymmetric synthesis', obviating any need for the chiral force of Nature active in biosynthesis conjectured by Pasteur. Fischer's conclusion left unsolved the problem of the origin of the primordial enantiomer from which stereoselective synthesis began, as he himself appreciated (Freudenberg 1966).

Chiral force fields

Pierre Curie (1894), in an analysis of the symmetry relations between a cause and its effect in physical phenomena, showed that each of the natural forces Pasteur considered dissymmetrical was, in fact, symmetrical to mirror-plane reflection. But a collinear combination of two complementary kinds of force, one rotatory (axial) and the other linear (polar), provides two possible chiral
force fields, the antiparallel combination being the mirror-image enantiomorph of the corresponding parallel combination. Rotatory and linear motion combined give a helical motion, right-handed if the axial and the polar vectors are parallel, left-handed if they are antiparallel. Similarly, a magnetic (axial) field and an electric (polar) field lose their individual mirror-plane symmetry in a collinear union. If the two components oscillate at a common frequency in an electromagnetic field, the two enantiomorphous combinations are represented by left- and right-circularly polarized light.

With his proposed structural explanation for optical isomerism, Le Bel (1874) suggested that circularly polarized light might favour the formation of one of the two possible enantiomers in a photochemical reaction. The surmise, supported by Curie, was provided with a physical basis by Cotton (1895), who discovered that an optical isomer in solution differentially absorbs left- and right-circularly polarized light (circular dichroism): for the enantiomeric molecule the differential absorption at the same wavelength is equal in magnitude but opposite in sign, analogous to the optical rotation (circular birefringence) in the longer wavelength region of optical transparency. Thus, a racemic mixture of photolabile enantiomers irradiated with circularly polarized light is expected to become optically enriched in the enantiomer with the smaller absorption coefficient for the particular hand of circularly polarized light employed (left or right).

Cotton searched for the expected effect, but without success, and the first authentic photoresolutions of racemic mixtures by irradiation with circularly polarized light were achieved by Kuhn (1930). Meanwhile, the surmise of Le Bel, reinforced by the studies of Curie and Cotton, led to a minor but enduring tradition that invoked circularly polarized sunlight as the original physical cause of an enantiomeric enrichment among the prebiotic biomolecules, which subsequently became elaborated to chiral homogeneity through competitive stereoselective reactions during the course of biochemical evolution.

Kuhn (1930) indicated a restriction on the photochemical theory of the prebiotic origin of biomolecular handedness. He showed that only monochromatic circularly polarized radiation, tuned to a particular light-absorption band of the racemate, discriminates between the two enantiomers, producing a photochemical change larger for one isomer than the other. Circularly polarized broad-band ‘white’ radiation, like sunlight, lacks discrimination, because the differential photoreaction at one wavelength is compensated by a converse differentiation at another: over the electromagnetic spectrum as a whole the chiral photodiscrimination between two enantiomers sums to zero.

Other restrictions on the theory of a photochemical origin of biomolecular handedness followed. Solar radiation has, in fact, a minor circular polarization of up to 0.5% at twilight, owing to scattering by dust particles. But the overall diurnal effect is very small, since the right-circularly polarized component in
excess at sunrise is almost wholly compensated by the left-circularly polarized component in excess at dusk. Similarly, the excess of right-circular light from the north pole of the Sun virtually cancels out the excess of left-circular light from the south pole in the total flux of solar radiation reaching the Earth (Mason 1988).

**Parity and its non-conservation**

During the 1920s it appeared that, on a time and space average, the classical chiral force fields characterized by Curie were even handed; singular circumstances—a particular time or place, or adventitiously monochromatic circularly polarized irradiation—had to be invoked to account for the origin of molecular handedness through their agency. The apparent even-handedness of all the forces of Nature was elevated to the principle of the conservation of parity in 1927 with the postulate that all physical causes and the laws linking them to the effects produced are invariant to spatial inversion through a coordinate origin (the parity operation) or, what is equivalent, they are unchanged by mirror-plane reflection.

The natural forces assumed to conserve parity included the newly discovered strong and weak nuclear forces responsible for α- and β-radioactivity, respectively. It was found observationally that the strong force conforms to the parity conservation principle but, from 1928, a few experiments involving the weak force gave puzzling results. Ultimately, the accumulation of anomalies led Lee & Yang (1956) to conclude that parity is not conserved in the weak nuclear interaction. They designed tests for parity violation and its occurrence was soon confirmed. The experiments establishing parity violation in the weak interaction showed that the fundamental particles have an intrinsic handedness or helicity. The electrons emitted in radioactive β-decay are inherently left handed, with the spin axis preferentially orientated antiparallel to the linear momentum direction, whereas the corresponding antiparticles, β-positrons, are right handed, with a preferred parallel alignment of the spin axis and the momentum direction. Although parity itself is violated in the weak interaction, the combination (CP) of parity (P) and charge conjugation (C)—the conversion of a particle into the corresponding oppositely charged antiparticle—is conserved in good approximation (strictly, time-reversal T must be included to give the more complete principle of CPT conservation).

The aspects of parity violation in the weak nuclear force that were initially studied involved charge-changes and particles moving with relativistic velocities, as in radioactive β-decay. Subsequent investigation of the neutral features led, around 1970, to the unification of the weak force with electromagnetism in the electroweak interaction, which gives rise to chirality effects in systems moving at non-relativistic velocities. In particular, the theory of the electroweak force predicts new chiral properties for atoms and molecules in their electronic ground
state or other stationary states. According to the principle of CP conservation, the negatively charged electron and the positively charged positron are CP mirror-image forms; the hydrogen atom, composed of an electron and a proton, has a CP enantiomer, made up of a positron and an antiproton. Viewed as chiral entities in the CP mirror, all atoms are expected to be optically active, giving an optical rotation proportional to the sixth power of the atomic number. This idea was pursued throughout the 1970s, and progressively increased accuracy in the measurement of optical rotation culminated in the early 1980s with the recording of an optical activity for heavy metal atoms in the gas phase (bismuth, lead and thallium) in agreement with the sign and magnitude calculated (Emmons et al 1983).

Again, according to the principle of CP conservation, a chiral molecule composed of normal atoms, such as L-alanine, has a true CP mirror-image analogue made up of anti-atoms in a counterworld of antimatter, but the terrestrial enantiomer with the standard particle composition (D-alanine) has properties dependent upon the electroweak interaction which are inequivalent because of the violation of the simple parity equivalence. The inclusion of the electroweak interaction in \textit{ab initio} quantum mechanical calculations of the binding energy in the electronic ground state show that the L-\(\alpha\)-amino acids, and the L-polypeptides in either the \(\alpha\)-helix or the \(\beta\)-sheet regular conformation, are slightly more stable than their respective terrestrial D-enantiomers. Similar calculations indicate that the parent triose of the D-sugar series, D-(+)-glyceraldehyde, and the salient furanose, D-ribose, are energetically stabilized relative to the corresponding L-enantiomers (Mason 1988).

The electroweak energy difference between the enantiomers of an amino acid or a sugar is small: it amounts to approximately \(10^{-14}\) J mole\(^{-1}\), corresponding to an excess of some \(10^6\) molecules of the stabilized enantiomer per gram mole of racemate (\(6 \times 10^{23}\) molecules) in thermodynamic equilibrium at the surface temperature of the Earth. Such an enantiomeric excess at equilibrium is not measurable as yet, but it has implications for dynamic reaction sequences remote from equilibrium.

Frank (1953) proposed a general mechanism for the evolution of biomolecular homochirality from a racemic basis by means of a flow reactor, in which each enantiomer acts as ‘a catalyst for its own production and an anticatalyst for the production of its optical antimer’. Darwin’s ‘warm little pond’, equipped with an input stream for substrates and an output stream for products, models such a flow reactor. The system is fed by an input of achiral molecules \(A\), which react reversibly with each enantiomer, L or D, with common rate constants \(k_1\) and \(k_{-1}\) to duplicate the enantiomer molecule:

\[
A + L(D) \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} 2L(2D)
\]  

(1)
In addition, the two enantiomers react together irreversibly, eliminating one another as the inactive side product, $P$, which constitutes, together with the excess enantiomers, the output of the flow reactor system:

$$L + D \rightarrow P$$

(2)

The system is stable, giving a racemic output with some inactive product $P$, as long as the input solution of achiral substrate remains dilute. At a larger input concentration the system becomes metastable, since the overall increase in the molecular populations results in greater competition between the enantiomers for the achiral substrate needed for self-propagation. The mutual elimination of the enantiomers (equation 2) now assumes more significance than their autocatalytic self-duplication (equation 1), and the system becomes hypersensitive to small perturbations that trigger the switching of the reaction sequences to production of one or the other single enantiomer.

Before the discovery of parity non-conservation, the direction of the switching appeared to be wholly a matter of chance, but afterwards it was demonstrated that the small electroweak energy difference (or concentration difference) between biomolecular enantiomers sufficed to determine which of the two single-enantiomer reaction sequences was adopted in the flow reactor at the metastable stage (Kondepudi & Nelson 1985). With typical rate constants (equations 1,2) and an allowance for thermal and photochemical racemization, the electroweak-stabilized enantiomeric series is selected with 98% probability if the passage through the metastable stage occupies some $10^4$ years in a flow reactor corresponding to a lake one kilometre in diameter and four metres deep.

The electroweak interaction differs from the classical chiral fields in its universality: the former has operated at all times and places, whereas the latter require special conditions for their chiral discrimination. The discovery that the electroweak force promotes the particular enantiomeric series selected during the course of chemical evolution, the D-sugars and the L-amino acids, means that biomolecular handedness on the Earth connects to more general chiral inequivalencies: thus, particles overwhelmingly predominate over antiparticles in the universe, owing to the violation of the approximate principle of CP conservation, within the exact principle of CPT conservation (Mason 1991).

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DISCUSSION

Kondepudi: The electroweak energy difference between the enantiomers of an amino acid corresponds to an excess of $10^6$ molecules of the stable form in a total of $10^{23}$. You may wonder how such a small difference, one part in $10^{17}$, can lead to differential production of L- and D-amino acids. How could the small difference have any noticeable effect when there are so many random fluctuations in factors, such as circularly polarized light, that could influence which enantiomer is formed?

The main point concerns an evolving system that comes to a critical point at which it has to choose between two alternatives. At that point it is extraordinarily sensitive. Even if a systematic bias is much smaller than the root mean square value of the fluctuations, the system is able to respond to that bias. The system does what electrical engineers call signal averaging. If there is a constant signal embedded in large random noise (the root mean square magnitude of which is much larger than the magnitude of the bias), by sampling the signal plus noise for a long enough time the system is able to pick out the small signal. For a random noise, the total output grows at a rate proportional
to the square root of the time for which it is gathered; for a systematic signal the output grows at a rate proportional to the time. After enough time, the total output of the systematic signal will exceed that of the random noise.

If we assume that during molecular evolution there came a point at which either L-amino acids or D-amino acids had to dominate (we don’t know why, we just have to assume that), then we find that evolutionary times of tens of thousands of years are long enough for the system to signal average the small bias, pick up this bias and respond to it (Kondepudi & Nelson 1985).

**Morgan:** In the competitive model, the D- and the L-morphs compete and destroy each other; is it envisaged that the D-forms compete with each other to the same extent or is the competition only intermorphic?

**Mason:** In the Darwinian reaction kinetics scheme of Frank, the competition is wholly interspecific. Molecules of the D-isomer annihilate only their L-enantiomers; they do not ‘fight’ other one another.

**Morgan:** Is there any justification for that?

**Mason:** At the molecular level there is none. In chemical reactions, molecules identical in all known respects—handedness, isotopic composition and so on—do compete with one another for substrate, but they do not ‘annihilate’ each other. In condensation reactions, identical molecules do eliminate one another, in the sense that they form dimers and polymers, but they are not ‘annihilated’ in the product formed.

**Wolpert:** Are you saying there is no basis for assuming competition?

**Mason:** No; but intraspecific competition in chemistry generally means only that the unsuccessful molecule lives to react another day, unlike the unsuccessful organism of intraspecific competition in the biological world.

**Kondepudi:** This question is something I have been pondering for many years. I was trained as a physicist, so I went to the Chemistry Department and asked if they could show me a system in which there was autocatalysis of L and D forms, and in which the two forms competed and destroyed each other. They did not know of any such system.

I have recently found that it can be accomplished very easily, in the crystallization of sodium chlorate, however, not with amino acids. The sodium chlorate molecule itself is not handed but the crystal has a definite chirality. That is similar to a non-chiral molecule changing to a chiral molecule. During crystallization there is a process of secondary nucleation. I found that if you crystallize sodium chlorate in a petri dish as usual, you find equal numbers of each form. But, if you stir the system constantly during crystallization, you find almost 100% of either L or D (Kondepudi et al 1990). The mechanism has to have two components, autocatalysis and competition. Otherwise, one enantiomer would not be able to dominate.

Autocatalysis arises from secondary nucleation. If you stir the solution, somehow one crystal is able to produce many others. This is an established fact, but the mechanism is not well understood. It is not simply breaking the crystal
into lots of little pieces. The competition comes because the first crystal is formed and it multiplies into many other similar crystals; this soaks up the solute so fast that the concentration drops rapidly and no other crystals can nucleate. The original crystal completely dominates the system. Competition need not be direct. In this case, I start with a system that has no bias and finish with 99.8% of the crystals having the same handedness. Which handedness will dominate is completely random.

Mason: One of my students, John Gould, obtained similar results with sodium uranyl acetate, which also forms handed crystals but is achiral in solution. He carried out a crystallization just before going on holiday; he obtained a large number of very small crystals that he stored in a covered beaker for later attention. On his return, he found a single large crystal in the beaker, and of course it was uniquely handed. Here, one crystal had grown by consuming smaller ones, through the processes of redissolving and recrystallization. Small crystals of both hands had been consumed, illustrating both interspecific and intraspecific competition.

Lewis: Are you saying that given what we know, you can deduce that evolution had to go in the direction of the particular handedness it has, or that there is a conceivable mechanism that might have had that consequence?

Mason: The latter. Solutions to scientific problems are never absolutely certain, only probable to a greater or lesser degree. Dr Kondepudi estimates a probability of 98% for the evolution of biomolecular homochirality by the comprehensive kinetic mechanism he has developed, based on the small electroweak energy difference between enantiomers, under the conditions he specifies.

Another feature of the acceptability of solutions to scientific problems is the degree to which they unify individual fields that were formerly unconnected. Thus, the dominance of L-amino acids and D-sugars in the biochemical world is now linked to the overwhelming predominance of particles over antiparticles in the universe by the electroweak interaction; they respectively exemplify the violation of parity (P) conservation and CP conservation within the overall principle of CPT conservation.

Brown: Is one of the consequences of this hypothesis that wherever we are going to find organic molecules in the universe they are going to be our kind of organic molecules?

Mason: Yes.

Brown: How disappointing.

Lewis: But is that proven or a speculative hypothesis?

Mason: It is well supported.

Wolpert: Then how do right-handed amino acids arise, for example?

Mason: Many bacteria synthesize D-amino acids for incorporation into their cell walls, but D-amino acids don’t occur in biochemically functional proteins. D-amino oxidases are widespread in higher organisms, presumably to remove
the D-amino acids produced by racemization or synthesized by bacteria. Penicillin is a relatively benign antibiotic because it interferes with only the incorporation of D-amino acids into the bacterial cell wall.

**Chothia:** As I understand this, originally, for $10^{17}$ D-amino acids there were $10^{17}+1$ L-amino acids. Professor Mason is arguing that the additional one eventually led to domination of the L-isomer.

**Wolpert:** The whole point about Darwinian evolution is that when one form dominates, the other simply disappears. In this case, I don’t understand why the D-amino acids have persisted.

**Mason:** D-amino acids are generated continuously by slow racemization from L-amino acids. The half-life of this racemization is about one million years at Earth surface temperatures; there are wide variations, depending on environmental conditions (dry solid or solution, and thence pH, ionic strength, catalytic co-solutes) and their chemical state (free or combined as di- or polypeptides). L-isoleucine contains two chiral centres, the $\alpha$- and the $\beta$-carbon atoms, the latter being very stable to epimerization. Normal racemization at the $\alpha$-carbon atom gives D-allo-isoleucine, which is not generally found in the normal metabolism of living organisms and can readily be detected by analytical chemistry. Even the small amount of D-allo-isoleucine formed during a human lifespan in teeth, where there is virtually no turnover of the amino acids in the proteins once the teeth are fully formed, is reliably detected. This can be used to show that putative centenarians are often somewhat younger than they claim. The established rates of racemization of the L-amino acids are widely used to date recent fossil bones, up to some 200,000 years old (Sykes 1988).

**Berg:** But if that racemization can happen in 80 years, why doesn’t it randomize the amplification mechanism discussed earlier?

**Kondepudi:** The dominance is maintained by the constant production of L-amino acids. They are removed by racemization but there is a constant input of L-amino acids from other compounds. The model takes racemization into consideration. For most amino acids the half-life of racemization is hundreds or thousands of years. Dentine is a rare example.

**Crow:** Isn’t this also used as an archaeological dating system?

**Mason:** Yes. It has been used to show that there were people in North America at least 40,000 years ago.

**Galaburda:** What establishes dominance in one direction in the first place? Is it dust in the atmosphere?

**Mason:** The scattering of solar radiation by dust particles in the atmosphere gives sunlight a circular polarization, particularly at twilight when the rays of the Sun traverse a maximum pathlength through the atmosphere. But the right circular component of solar radiation in excess at sunrise virtually equals the excess of the left circular component at sunset, and the net effect over the course of a day is vanishingly small. One can envisage a pool of racemic amino acids on an east-facing slope that catches sunlight only at dawn. In prebiotic times,
right circularly polarized ultraviolet radiation, which is now filtered out by the ozone layer and the oxygen in the atmosphere, could have produced a differential photolysis of the two enantiomers, leaving the L-amino acids in excess.

Analogous views of the origin of biomolecular handedness held between 1900 and 1980 that were derived from the characterization of classical chiral force fields by Pierre Curie were similarly dependent on special conditions—particular times and places, dawn or dusk, the northern or southern hemisphere, and so on. The electroweak interaction is a universal force: it has operated at all times and places; no special conditions are required to produce its determinate effects.

Wood: Don’t we have to worry that the origin of life may not have been an average process but may have happened in a unique situation?

Mason: One can choose: particular times and particular places, or a universal force that’s been in operation since the universe began.

Frankel: Presumably, there is some deterministic process that resulted in a predominance of the L-amino acids; these then became incorporated into the most important molecules in organisms. A secondary racemization provided D-amino acids, which appear in certain relatively unusual molecules such as the cell walls of bacteria. If we imagine some other planet on which life is originating, what would prevent the secondary racemization leading by chance not to some peculiar, relatively minor molecule but to the informational equivalent of a nucleic acid?

Mason: The world of ‘chance’ is open ended; in it, ‘anything goes’. The concept of ‘chance’ as a kind of even-handed nescience becomes useful principally when it is tamed statistically into a normal-error or other type of distribution with determinate large-scale expectations, as in the Maxwell–Boltzmann distribution of energy over an assembly of gas molecules, or in the population genetics of a species in a given ecosystem.

McManus: Given that there are D-amino acids on our Earth and that most organisms use L-amino acids for building their bodies, surely there is a point at which it becomes selectively advantageous for an organism to build its body with the D-amino acids which are around because then it couldn’t be eaten by the other organisms?

Mason: That may have been the original selective advantage of the microbes that incorporated D-amino acids into cell walls. But then fungi evolved penicillin and other antibiotics which countered that advantage. The D-amino acids do not occur in any functional metabolic proteins, such as ribosomes or enzymes. They are found only as a structural component of bacterial cell walls, and in other products of secondary metabolism, such as antibiotics.

Thwaites: But in terms of biomass that is a very large amount. Are you implying that the relative amounts of D- and L-amino acids in the bacterial cell wall has changed over a long period of time?

Mason: The ratio of D- to L-amino acids in the bacterial cell wall probably has changed over time. Where it can be measured with any confidence, i.e. over
the last 200,000 years or so, the ratio records only the slow racemization towards an equimolar equilibrium. In the early microfossils, which date back about three billion years, the residual organic material is in the form of a complex carbonaceous polymer, kerogen, and little evidence remains of the type of organic molecules from which this derived.

Galloway: It's not true that there are no functional D-amino acids. There have been reports of D-amino acids in neuropeptides, for example dermorphin. Some dipeptides may also include D-amino acids: these would not be coded for as parts of proteins but would be created by specialized enzyme activity.

Also, antibiotics are often composed of alternating sequences of L- and D-amino acids, for example gramicidin (produced by Bacillus brevis).

Mason: The neuropeptides and the antibiotics are not produced universally by all living organisms: they are products of specialized secondary metabolism, like the alkaloids and terpenes. Some species of the Camphor laurel produce D-camphor; other species produce L-camphor.

During the 1930s there was a vigorous debate on the significance of D-amino acids found in protein hydrolysates from human cancer cells. By 1940 these were shown to be artifacts of the isolation procedure that resulted in some racemization (see Gause 1941).

Corballis: Does the CPT conservation imply that the ultimate asymmetry is time? If time went the other way, would I scratch my head with the other hand? Time is the most obviously asymmetrical parameter.

Mason: Perhaps when the Big Bounce occurs and the universe begins to contract, you will use the other hand.

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Macromolecular asymmetry

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Abstract. The helix is the most common and the most readily recognized example of an enantiomorphic structure. Helical proteins and DNA are good examples of structures where a clear explanation can be provided as to why they adopt one hand or the other. Proteins and DNA are composed of chiral building blocks, amino acids and nucleotides, respectively. Only the L-amino acids occur in proteins; this uniformity of handedness is a prerequisite for helix formation and thus, one could argue, for the development of higher life forms. Helical proteins form higher order helical structures, from collagen and viral capsids to cotton fibres.

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I have never been able to decide whether the problem of left–right asymmetry is very deep or quite trivial—and in a sense that is what keeps me interested in it.

What is undoubtedly true is that although scientists may find the question interesting, artists do not. For example, Fig. 1 shows an engraving of Fragonard’s The Swing. It is a mirror reflection of the original painting that is part of London’s Wallace collection. The reason for its being reversed is easy to find—the engraver made a plate identical to the original painting, which then printed a reversed image. However much artists care about colour, mass, form and realism or drama, they do not seem to care which way the pictures actually point, i.e. their right–left asymmetry.

My earliest interest in the problem I can trace to reading (Alice) Through the Looking Glass. A prominent feature of the book is its numerous examples of helices. The picture by Tenniel shown in Fig. 2 contains toves, which are badger-like animals with corkscrew noses and tails. These are, as far as I know, the only pictures of toves and the helices are left handed.

The helix is biology’s favourite shape. Because of its elementary geometry and distinctive appearance it is also the clearest instance of an enantiomorphic object—a helix and its mirror image are identical in all respects except their screw sense. This is a distinction that can be ignored from the points of view of pure geometry and pure group theory but any helical structure is available as either hand.
The potential for having a mirror-reversed 'twin' is not peculiar to helices with their screw symmetry; it is characteristic of any object that possesses no inverse symmetry elements. The simplicity of the helix makes it most suitable for demonstrating the principles underlying the existence (or not) of mutual mirror images. Conklin (1903) wrote in his paper, 'The cause of inverse symmetry' that 'inversion of symmetry' (i.e. production of a mirror image) in animals, 'with its profound implications for embryology, is clearly seen in gastropods' (which are roughly helical) 'though doubtless taking place in other animals where it is obscured'.

The agreeable economy of the helix makes it the preferred solution for innumerable problems of growth, form and function in living things. Because it is so common, found at every anatomical level across about nine orders of magnitude (Table 1), it is possible to disentangle to some extent the mechanical or structural design principles behind the helix from the large number of ways the design can be realized. One reason for the popularity of the helix can be found in Needham’s (1936) rather apt description of biology as 'largely the study of fibres'. Add to this the idea articulated by Crane (1950) that 'any structure which is straight or rodlike' (a category that includes fibres when the length greatly exceeds the diameter) 'is probably a structure having a repetition along a screw axis', i.e. a helix, and the central role played by the helix in biology is clear. More recently, Wainright et al (1976) have pointed out that the hollow cylinder provides the most common design for body walls on every scale. The cylinder lends itself to a helical mode of construction whether using discrete subunits, as in the cylindrical viruses, or helical winding, as in animal bodies and plant cell walls (Fig. 3).

Biological macromolecules: helices of one hand only?

The emergence of the helix as the structural paradigm of molecular biology can be traced to Linus Pauling: 'rolling paper scrolls on a sick bed in Oxford in 1948 before the helix was built as a model structure by Branson and Corey in Pasadena in 1950' (Hodgkin & Riley 1968). Before then the helix was not taken very seriously; afterwards it became the most common and important structure for those interested in big biological molecules and recognized as 'the classic element of protein structure' (Richardson 1981). In 1953, biology's most famous helix appeared in print for the first time with the publication of Watson and Crick's paper on the structure of DNA.

Questions that arose immediately and have continued to be asked up to the present day are what handedness these molecular helices would adopt—and why. Early structural work on fibrous proteins and nucleic acids relied on fibre diffraction, which could not readily distinguish helical hand. Electron microscope studies of helical viruses, like tobacco mosaic virus, and helical organelles, such as microtubules and bacterial flagella, suffered from a similar deficiency although for a rather different reason. The electron microscope could
FIG. 1. "The Swing" by Fragonard. The picture on the left is an engraving (courtesy of The British Museum). The original is shown on the right (courtesy of The Wallace Collection, London).