

Chapter 6: Hypernotes

WWW 6:1

Jonathan Miller has pointed out how very strange it is that Alice, despite being so keenly observant of almost everything in the looking glass-room, has failed to notice the one thing which would tell her that it was indeed only a mirror reflection, the image of her mirror-reversed self in the other room (Miller, 1998 p.120).

Martin Gardner (1990b p.124) comments that “Lewis Carroll could hardly have been aware of how profound a question his Alice was raising”. I wonder if this is so. *Through the looking glass* was published in 1871. Pasteur’s work on tartaric acid was published in the 1840s, and by 1874 Van’t Hoff had published his theory of stereochemistry. In 1860 Pasteur had even speculated what would happen if the world was inverted left-right:

“Perhaps a new world would be presented to us. Who could foresee the organisation of living beings, if the cellulose, which is right, should become left, if the left albumen of the blood should become right? There are here mysteries...” (Meister, 1965 p.113)

Given Pasteur’s immense popularity during his life time it is at least possible that Carroll read this or similar comments. Heilbronner and Dunitz (1993 pp.85-6) also point out that a close friend of Carroll was the chemist Algernon G V Harcourt, also a Fellow of Christ Church, and who would probably have been aware of recent work by Wislicenus on stereoisomers of lactic acid, which is obtained from the fermentation of milk.

WWW 6:2

A peptide consists of two or more amino acids joined together. Oligopeptides have been defined (Scott & Eagleson, 1983 pp. 437-438) as those with 10 or fewer amino acids, polypeptides with more than 10 amino acids, and proteins as those with more than about 100 or so amino acids. It is all a bit biologically arbitrary and I have tended, rather loosely, generically to call them all proteins, but I sometimes use the term peptides where it seems more appropriate.

Although it is a commonplace, particularly after the Human Genome Project, to regard DNA as the key 'molecule of life', it is really the proteins, with their rich diversity of form which create all the tissues of life. DNA has an important role mainly because it can specify the complicated sequences of those proteins in a replicable form. If one had to put a bet on whether it would be easier to create life without DNA or life without proteins, then there seems little doubt that the DNA is less important.

☞ WWW ☞ 6:3

The simplest and smallest of the amino-acids, glycine, is an exception in not coming in enantiomeric forms, since the R group is a hydrogen, meaning there are two hydrogen atoms on the carbon atom and hence the molecule is not chiral.

Although I talk about D- and L-amino acids, there is a technical issue here which I have slid over, preferring for simplicity to use D- and L- throughout the main text. Since the time of Pasteur, isomers have been called D- (dextro-rotatory) or L- (laevo-rotatory) according to whether they rotate polarised light to right or left. Sometimes they are referred to as (+) and (-), or d- and l- with the same meaning. A fundamentally different form of nomenclature looks at the precise, absolute layout of the various chemical groups around the carbon atom which is the chiral centre of the molecule, and the two types are referred to as R- (rectus) and S- (sinister), from the Latin for right and left. There is no necessary correlation between being D- and being R-, or between being L- and being S-, and all possible combinations can occur, for instance in the amino-acids, where all are S- in the absolute sense but a few rotate polarised light to the right (Tucker, 2000). Pasteur himself realised the difference between absolute chemical structure and rotation of polarised light when he showed that what we should strictly call R-tartaric acid rotated light to the right (D) when dissolved in water but to the left (L) when dissolved in hydrochloric acid (Nicolle, 1962 p.28). A chiral centre is defined according to the atomic mass of the four substituents attached to the carbon atom.. Looking at the carbon atom from the side opposite to the substituent of lowest atomic mass, if the remaining three substituents decrease in mass clockwise then the chiral centre is R, anticlockwise and it is S (Lamzin, Dauter, & Wilson, 1995 p.830).

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In his definition, Kelvin continues: “Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or 'allochirally' similar (but heterochirally is better). These are also called 'enantiomorphs', after a usage introduced, I believe, by German writers. Any chiral object and its image in a plane mirror are heterochirally similar” (Kelvin, 1904). Although Kelvin’s definition still stands for static objects, it does not cope well with moving objects, and a more recent definition says, “True chirality is exhibited by systems existing in two distinct enantiomeric states that are interconnected by space inversion, but not by time reversal combined with any proper spatial rotation” (Barron, 1996 p.165).

☞ WWW ☞ 6:5

Auden's Quant asks his image about Looking-Glass world:

“My deuce, my double, my dear image
Is it lively there, that land of glass
Where song is a grimace, sound logic
A suite of gestures?” (Mendelson, 1976; *The Age of Anxiety*, p.346).

Martin Gardner (1990b p.124) pointed out that although the alcohol will taste the same, the many congeners which give the interesting flavours to most alcoholic drinks are probably chiral, and the drink would probably not therefore taste the same.

The error about D- and L-limonene occurs frequently on the Internet, both in educational sites, see www.americanhistory.si.edu/hosc/molecule/04exp.htm and www.chem.swin.edu.au/courses/swin/stereo/enan.html. The source for this common error is probably Gardner (1990b p.123), who says “It was recently discovered that the differences in the smell of oranges and lemons is caused by differences between right and left forms of limonene”. Although earlier in the same paragraph Gardner talks about an article in *Scientific American* on the topic (Amoore, Johnston, Jr., & Rubin, 1964), the paper mentioned actually does not discuss orange and lemon specifically, although it does say some stereoisomers smell different, but without specific examples. The error is surprisingly prevalent (e.g. Hegstrom & Kondepudi, 1990a), and I confess to being responsible for it creeping into an article in *Wellcome News* (Fricker, 1999).

The analogy of a lock and key to describe how enzymes interact with their substrates was first used by Emil Fischer in 1894 (Mason, 1989 p.186).

Many complex biological molecules on which smell depends come in more than two forms. Although it is usual to think of chiral molecules as just L and D, that is only the case if there is a single carbon atom which has four different groups attached to it. If a molecule has two such carbon atoms then two chiral forms can occur at each carbon, giving four different forms, and so on.

There is an interesting variant on the question of symmetry in the keys for Yale locks. Most such keys for front doors require the key to be put into the lock the correct way up. Car door keys, in contrast, are now often made so that they can be put in either way up, to save awkward fumbling in the dark or the cold. However both sorts are still chiral, and their mirror images would not work.

WWW 6:6

Although D-thyroxine has been reported to be effective in suppressing normal thyroid activity (Bantle et al., 1984), there seems a problem with all such studies in that commercially available D-thyroxine is contaminated with several percent of L-thyroxine, which is of course active (Young-WF et al., 1984). This may explain the claim made by Gardner (1990b pp.123-4) that D-thyroxine reduces cholesterol.

WWW 6:8

One can appreciate the scale of the advances in synthetic chemistry by looking at the journal *Tetrahedron*, which gets its name from the spatial layout of the carbon atom's four bonds. In 1990 a new section was started, *Tetrahedron: Asymmetry*, devoted to the synthesis of stereoisomers; already its densely packed pages fill one and a half shelves of my university's library.

For more about the award of the 2001 Nobel Prize in Chemistry see Adam (2001) and the Nobel Prize website (www.nobel.se/chemistry/laureates/2001/public.html). For recent advances in chiral synthesis see Gómez and Waymouth (2002).

WWW 6:9

The problem of thalidomide's racemisation has been forcefully put in several places (Wnendt & Zwingenberger, 1997, Winter & Frankus, 1992), and there seems little doubt that thalidomide racemises *in vivo* very quickly (Eriksson et al., 1995; Eriksson et al., 1998). There are many examples of the mythology about thalidomide, for instance by Dr. Philip Emeagwali at www.inventors.about.com/library/weekly/aa111097.htm, by Professor Michael Chong at www.adm.uwaterloo.ca/infonews/release/1997/186%20New%20ways%20to%20make%20molecules,%20November%202024,%201997.html, at www.bgsm.edu/graduate/asymmetry.html, by Hegstrom and Kondepudi (1990a) and by de Silva (1995). The Internet does however have more accurate versions of the story, as for instance at the American Medical Association web-site www.ama-assn.org/special/hiv/newsline/briefing/thalido.htm. There are also suggestions that the rapid racemisation may be avoidable in chemically modified forms of the drug.

The story of the different clinical effects of the two forms of thalidomide is cited by MacDermott *et al* (1996 p.1442), who quoted a paper by Blaschke *et al* (1979) as showing that while L- and D- forms are both hypnotic, only the L-form was teratogenic. The Blaschke *et al* (1979) paper does not in fact discuss the hypnotic effect at all, but does find a clear teratogenic effect of L-thalidomide but not D-thalidomide. Early studies had wondered whether some of the toxic effects of thalidomide might be due to its breakdown products "containing amino acid residues of the unnatural D-series" (Fabro *et al.*, 1965). A subsequent paper (Fabro, Smith, & Williams, 1967) however found no differences between L- and D-thalidomide in hypnotic or teratogenic effect (although mysteriously the racemate was of very different toxicity to the pure enantiomers (Knightley *et al.*, 1979 pp.14-20 & 264), and there is now some scepticism that thalidomide is chiral in its effects (Winter & Frankus, 1992). More recent work suggests that more chirally stable homologues of thalidomide are teratogenic only in the L-form (Wnendt *et al.*, 1996, Schmahl *et al.*, 1996, Heger *et al.*, 1994). There is also some support for D-thalidomide being more hypnotic than L-thalidomide (Hoglund, Eriksson, & Bjorkman, 1998).

Although it is generally assumed that thalidomide has been banned and is never used, in fact it is being used under very strictly controlled conditions for the treatment of certain severe immune problems, such as erythema nodosum leprosum in leprosy, and Behçet's disease. It seems that both the D- and L-forms of thalidomide analogues have the immunomodulating activity, with the L-form being slightly more effective (Wnendt *et al.*, 1996). Thalidomide has recently been licensed by the US Food and Drug Administration, under very strict conditions, for treating a range of otherwise untreatable conditions (Horton, 2001).

WWW 6:10

The twenty amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tyrosine, tryptophan, serine, proline, threonine, cysteine, asparagine, glutamine, lysine, histidine, arginine, aspartate, and glutamate (Nelson & Cox, 2000). Some amino-acids are specified by more than one combination of three bases in the triplet code. There is also evidence that occasionally the stop codon, UGA, in bacteria and in mammals, can specify a twenty-first amino acid, selenocysteine (Atkins & Gesteland, 2000). A recent advance has also shown that in *E. coli* it is possible to create a novel transfer RNA which reads the codon UAG, which is normally a nonsense codon, and instead incorporate a novel,

non-canonical amino acid, *O*-methyl-L-tyrosine into the proteins produced (Böck, 2001; Wang et al., 2001). An interesting speculation is whether such technologies might one day allow D-amino acids to be incorporated into proteins.

The fact that the sugars we consume and of which we are composed are mostly in the D-form has made some people wonder about the L-sugars, and in particular to speculate that they may be useful precisely because they are *not* metabolised. If they cannot be metabolised it must also be the case that neither can they be converted into fat, the fate of excess sugar. Since L-glucose also tastes as sweet as ordinary D-glucose, some people have argued that it would be the perfect food additive – sweetening without fattening. It is a nice idea, but nature is not fooled that easily. The L-glucose may well not be metabolised but it has to go somewhere. It is a small molecule and therefore will be absorbed through the wall of the bowel, much is then removed in the liver, and the rest then circulates in the blood before being excreted by the kidneys. And in the sort of quantities that are involved in a typical Western diet, that is a lot of sugar to excrete, and it would almost certainly have bad effects on the kidneys and bladder, with stones and infections being real possibilities amongst others (Clemmit, 1991; Gram, 1986).

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There are good reasons other than purely curiosity, for looking at D-proteins, one of which is that they can help in working out three-dimensional protein structures, which is always difficult, not least because all the standard methods of X-ray crystallography suffer from the ‘phase problem’. Using crystals composed of a racemic mixture of the D- and L-protein reduces the number of possible phases from a very large number down to two, since the system has symmetry restored to it (Lamzin, Dauter, & Wilson, 1995, Petsko, 1992).

The D-protease (Milton, Milton, & Kent, 1992) was not the first D-protein to be synthesised, but it was the first to have a chiral substrate (Petsko, 1992).

There is a theoretical concern that since the D-protease is constructed from matter, rather than from anti-matter as should a true, complete enantiomer, then it ought to be less efficient or in some other way different from the L-form due to the asymmetry of the weak interaction. However theoretical calculations suggest that the protein would have to be bigger by about ten orders of magnitude (i.e. 10^{10}) before an effect would show (Brewster & Laskowski, 1992).

☞ WWW ☞ 6:12

Spontaneous racemisation of amino acids is one of the main reasons why it has in the past been difficult to get an accurate measurement of the extent to which D-amino acids occur naturally, since early techniques for breaking down proteins into the amino acids of which they were made up, also produced racemisation.

Although it is probable that all amino acids can spontaneously racemise, it seems that aspartic acid is particularly vulnerable, being the predominant D-amino acid found in red blood cell proteins, where it arises either by direct racemisation of L-aspartic acid, or by deamidation of L-asparagine (Ingrosso & Perna, 1998).

It has been estimated that D-Aspartate accumulates in the lens of the eye at a rate of 0.14% per year. The technique of measuring aspartic acid in the lens has allowed estimates of the age of bowhead whales, some of which appear to be over two hundred years old (George & et al, 2000). The amino acid clock does seem to be influenced by temperature, and as a result it has also been used to estimate temperature (Miller, Magee, & Jull, 1997). There are some minor problems with the dating from Ötzi, which the authors describe (Lubec, Weninger, & Anderson, 1994), because an Egyptian mummy, also 5200 years old, has only 24% D-amino acid. It is not clear whether it is Ötzi or the mummy which is anomalous. Nevertheless the general principle of the method is still clear enough.

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The essential amino acids in humans are leucine, iso-leucine, lysine, phenylalanine, methionine, cysteine, threonine, tryptophan, valine.

Proteases work by breaking the bond between one amino acid and the next, which is of the form -CO-NH-. By splitting a water molecule, H₂O into H- and -OH, and adding the -OH to the -CO- to form -COOH, and the H- to the -NH- to form NH₂-, the bond is broken. Since water is added the process is known as hydrolysis. A detailed account of the mechanisms can be found in Zubay (1998a).

The L-lactose and other L-sugars in the Looking-glass milk would also not be absorbed, and would probably contribute to diarrhoea, mostly by an osmotic effect which causes water to be sucked into the bowel.

☞WWW☞ 6:15

To give an example of D-amino acids in foods, unpasteurised raw milk has about 1.5% D-amino acids, whereas the proportion rises to 2.1% in powdered milk, 3.2% in evaporated milk, and 4.9% in infant formula milk (Man & Bada, 1987 p.214). The proportion of D-amino acids is particularly high in food cooked at high temperature with alkali, such as corn chips and tortillas (Man & Bada, 1987). It is also probable that irradiated food has a higher proportion of D-amino acids.

The rats kept in a germ-free environment actually have lower levels of D-amino acid oxidase and, by inference, of D-amino acids (Bender, 1985).

Sir Hans Krebs (1900-1981) who discovered D-amino acid oxidase, received the Nobel Prize in Physiology or Medicine in 1953.

Free D-amino acids can be found in human blood, and the levels are higher in the elderly, and in those with kidney disease, suggesting that the D-amino acid oxidase in the kidney may be impaired (Nagata et al., 1987). The effects of ageing are probably a secondary consequence of impaired kidney function.

D-amino acid oxidase is intriguing for another reason, because the active site into which the D-amino acid binds is the precise mirror image of the binding site of another enzyme called flavocytochrome *b*₂ (Mattevi et al., 1996). Producing a binding site which is the mirror-image

of another is a peculiarly difficult problem if one cannot simply substitute all the L-amino acids with D-amino acids, and it is intriguing that evolution has managed to achieve this task.

☞ WWW ☞ 6:17

The need for all these elaborate defensive and aggressive measures comes from one of the great truths of Life, the Universe and Everything. Life is a very dangerous, fragile, vulnerable business. One mistake and any organism ends up as part of some other organism, having been eaten. Very small organisms are particularly vulnerable, being merely thin-skinned bags of a delicious and nutritious soup of fats, carbohydrates and proteins. Rule number one is therefore to avoid being eaten, and organisms have developed a myriad of ways to achieve that aim. Rule number two is pretty similar: avoid being infected, which actually is only being eaten, but this time slowly from within, rather than quickly from without. Almost all organisms, however simple, therefore have a myriad of methods of making themselves unpalatable or inedible, or for killing invaders. All will deter predators.

By one of those coincidences for which history is renowned, in 1928, the same year that Fleming discovered penicillin, another very distinct sort of antibiotic was discovered by Rogers – it is called nisin, is licensed as a food additive in the United States, and has probably been used informally by humans to preserve food since the beginnings of recorded time. It was the first of a class of antibiotics known, rather confusingly, as the lantibiotics — and, No, that ‘l’ is not a typo. They are called lantibiotics because they all contain the very strange amino acid lanthionine (Hansen, 1993), which consists of two alanine molecules joined together by an atom of sulphur, Ala-S-Ala.; and not surprisingly, since they are included here they all contain a hefty dose of D-amino acids as well. The second lantibiotic, subtilin was not discovered until 1948, after which there was a long gap until suddenly a dozen were identified at the end of the 1980s. To see what is so different about the lantibiotics, we need to think about how an organism might go about producing a conventional antibiotic. The problem is that these more traditional antibiotics contain unusual, if not distinctly bizarre, amino acids, and therefore they cannot be produced by ribosomes which simply read off the instructions from the genetic code in the DNA. Two types of solution are possible. One is to ignore the DNA and instead to set up a specific multi-enzyme complex which acts as a one-off production line for the antibiotic. (Of course the enzymes themselves are coded for in the DNA and produced by ribosomes in the usual way, but that is very different from the way in which the lantibiotics are produced). A one-off production line works but it is not easy to modify the system effectively and quickly. Worse still from a human perspective, if we want new antibiotics to replace old, ineffective ones rendered useless by acquired resistance, we can only go off searching for yet more different, yet more unusual organisms in the hope that they will provide some novel antibiotic substances. The alternative way of producing an antibiotic, the way of the lantibiotics, is to encode them in the DNA as a sequence of base pairs which the ribosomes can translate into a peptide, albeit one containing the standard, boring set of twenty L-amino acids. That peptide can, however, then be acted upon by a series of enzymes in what is called post-translational modification, replacing some of the amino acids with more exotic ones, and making some of the L-amino acids into D-amino acids. The advantages of this for the organism are enormous. Firstly, most of the assembly process merely uses the existing ribosomal machinery. And secondly, a small change in the genetic code, the very stuff of which evolution is made, can produce small changes in the lantibiotic, so that natural selection can readily fine tune the lantibiotic for changes occurring in the organism’s environment or predators. That also is the advantage for humans as well,

since we can use artificial selection and the methods of genetic engineering to create changes in the lantibiotics to make them suitable for our needs, rather than the needs of the bacteria. They may well be the future for new antibiotics, which cannot forever go on being found using the old methods, which relied heavily on chance

Another novel approach to producing antibiotics, the creation of nanotubes which pierce the bacterial cell wall, thereby releasing the cell contents, also relies on using D-amino acids, which both resist protease action and also, when paired with L-amino acids, produce a symmetric tubular molecule (Gura, 2000).

☞WWW☞ 6:18

In 1992, fifty-seven years after he entered the University of Pavia as a student, Erspamer published a full-length review of the opioid peptides he had discovered (Erspamer, 1992).

Erspamer's personal feelings are rarely expressed in academic papers, but their very scarcity makes them all the more affecting. Science and scholarship are not carried out in an emotional vacuum, and as Freud said, all behaviours, however seemingly simple, are always over-determined, with many and complex motivations, often with their hidden defense mechanisms. Whilst reading around in preparation for this book, I came across the second edition of George Dumézil's *Mitra-Varuna*. Its introduction, written, in January 1947, also ends on a note of almost unbearable sadness, which so echoed that of Marcel Mauss' description of Durkheim's decimated research group (see chapter 2), that I feel I must quote it, 'lest we forget':

"I shall always retain a particular fondness in my heart for the year 1938-39; but it is a memory peopled by ghosts. ... Every Thursday in the lecture hall [in Paris], beside Roger Caillois, Lucien Gerschel and Elisabeth Raucq, I would greet our gracious colleague Marie-Louise Sjoestedt, whose pupil in turn I became on Wednesdays when she taught me Welsh and Irish; she was not to survive France's first misfortunes. Pintelon, an assistant professor at the University of Ghent, was destined to perish in uniform while on guard in Belgium, even before the invasion. Deborah Lifschitz, from the Musée de l'Homme, so kind hearted and intelligent, was doomed to the horrors of Auschwitz. Other young faces were destined for other ordeals...". Dumézil, 1988.

☞WWW☞ 6:19

The title of the 1999 paper, "What peptides these deltorphins be", (Lazarus et al., 1999), is said by the authors to be a paraphrase of "What fools these mortals be", which is attributed to Seneca, although it is also an exact Shakespearean quote, from *A Midsummer Night's dream* (Act 3, scene 2).

☞WWW☞ 6:21

The dermorphins act on the μ (mu) opioid receptors, and the deltorphins on the δ (delta) receptors. As yet no amphibian peptides have been found that act on the κ (kappa) opioid receptors.

Since the deltorphins are active after injection into veins, passing across the blood-brain behaviour, these could well be the designer drugs of the future. Instead of heroin and morphine originating in fields full of poppies in hot, tropical countries, after which they are harvested, purified, and then transported halfway around the world, illegally crossing multiple

frontiers, before ending up on the streets of our cities, such drugs could be created by anyone with the basic laboratory facilities to synthesise a peptide consisting of seven amino acids, the only technical difficulty being the inclusion of the D-amino acids. And much, much smaller quantities than heroin and morphine would be required. It is a frightening prospect, but, at always, Pandora's box contains many things, and the lid can never be put back on. It is worth remembering that humans have always searched hard for psychoactive drugs – and it is a pretty strange thing, when one thinks about it, to smoke or inject the processed juice of a ripe poppy.

☞ WWW ☞ 6:22

A problem for most ordinary biochemical techniques is that they do not distinguish D- and L-amino acids. Indeed once the sequence of dermorphin was discovered a peptide was synthesised and found to be completely inactive, and only after careful checking did it emerge D-alanine rather than L-alanine was needed. The moral is that no amount of scanning through the genomic data banks, or looking at protein digests or using mass spectroscopy will reveal whether D-amino acids are important in proteins. The only check is to build the protein from scratch and see if it works. If it doesn't then a D-amino acid could be lurking (Scaloni, Simmaco, & Bossa, 1998).

There are also D-amino acids in proteins in *Mytilus edulis* (Volkman & Heck, 1998 p.83), the bivalve mollusc, *Mytilus edulis*, (Volkman & Heck, 1998), the African giant snail, *Achatina fulica*, the snail, *Helix pomatia* (Yasuda-Kamatani, 1998), the crayfishes, *Procambarus clarkii* and *Procambarus bouvieri* and the lobster, *Homarus americanus* (Huberman & Aguilar, 1998).

A photograph and other information about *Conus* can be found at www.ncrr.nih.gov/newspub/mar97rpt/snail.htm.

The witches in *Macbeth* would have recognised the essential recipe for finding D-amino acids, with “poisoned entrails” and “toad[‘s] ...sweltered venom”, “eye of newt, and toe of frog”, and “adder’s fork, and blind-worm’s sting”. D-amino acids do seem to be disproportionately involved in nasty, toxic substances for which the modern pharmaceutical industry can find all sorts of interesting uses. But then most of the effective drugs are simply poisons used in small enough doses to be helpful. If drugs could not poison at high doses then they probably would not have any useful physiological effect in conventional doses. Finding effective drugs has never been easy, and doctors and pharmacologists have looked in unlikely places – William Withering found digitalis in the foxglove, atropine comes from the deadly nightshade, aspirin came from the bark of the willow tree, and of course penicillin comes from a mould. The vast majority of such finds have been from plants or fungi, and very few have come from animals, the most obvious exception being curare, the muscle relaxant which also came from frogs. That situation is however changing, and animals are now being looked at systematically. Dr David Newman of the National Cancer Institute in America put it very nicely indeed: “If you are fat, fleshy, brightly coloured and slow moving, I want to see you. There’s something in you, on you, or travelling with you that stops you from being eaten” (Gratzer, 2000). That description fits the snails well, and also the many frogs and toads of the Amazon basin which are typically brightly coloured. In the biological warfare that constitutes the fight for survival between hungry species, “the creature with the best chemistry set wins”(Gratzer, 2000). D-amino acids are yet another variant in that

chemistry set, and while one's enemies are not using them then they are a very powerful weapon, particularly when used to make venoms which are potent poisons acting quickly on an enemy's brain to paralyse or convulse them. It is not of course easy using such potent weapons. They have to be produced, they have to be stored, and when used they have to be replaced, a process often taking days or weeks and leaving the animal vulnerable. There is also the problem of making sure that you do not inadvertently poison yourself or your nearest and dearest. Perhaps that is why relatively few species have developed these intricate forms of defence.

☞ WWW ☞ 6:23

There is something seemingly rather arbitrary about which of anything we call right or left. Is there then any deep sense in which amino acids are L and sugars are D? Yes, is the answer. The German chemist, Emil Fischer in the 1880s worked out the structural (as opposed to the optical) chirality of the amino acids and sugars. He started with the simplest chiral organic molecule, glyceraldehyde, which has -H, -CHO, -OH and -CH₂-OH attached to its central carbon atom. He called one version D-glyceraldehyde, according to the organisation of the groups around the central carbon atom, and then worked out whether all of the other organic compounds, including amino acids were structurally the same or reversed with respect to the carbon atom. The sugars were the same structure as the D-glyceraldehyde and the amino acids were the opposite, and hence were the L-forms.

There is another argument lurking beneath the surface of homochirality which asks whether there is any advantage to building systems entirely from asymmetric components (rather than from symmetric ones). Evidence from computer simulations of complex autonomous replicators suggests that they are easier to build with less complex rules if the replicators are themselves symmetric (Sipper & Reggia, 2001).

☞ WWW ☞ 6:24

The geneticist JBS Haldane put both the question and the answer very clearly:

"[A biochemist who] finds the same quite complex molecules in all plants and animals, can hardly doubt their common origin. There may be some reason in the chemical nature of things why all living creatures must contain glucose. But there appears to be no reason, other than common ancestry, why they should all contain dextrorotatory glucose, and none of them its mirror image". (Haldane, 1932 p.146).

In other words, as Leslie Orgel said, "the earth could equally well have been populated by D-organisms" (Orgel, 1973 p.167). Similarly, Murray Gell-Mann, the Nobel prize-winning theoretical physicist, suggested that "the biochemical left-right asymmetry is a frozen characteristic of the ancestor of all surviving terrestrial life, and ... it could just as well have turned out the other way". It is nothing but a "frozen accident" (Gell-Mann, 1995 p.229)

The Encyclopaedia Britannica article also comments that, "Whether left- or right-handed activity was adopted was probably purely a matter of chance...". And likewise Martin Gardner (1990b p.150) comments that "Whichever handedness predominated might gain a competitive advantage simply by virtue of its larger numbers". It must though be said that Gardner is somewhat out of date, even in his revised edition of 1990, since he still says that the Murchison meteorite has a racemic mixture of amino acids.

The form of the argument is not new, and is exactly akin to that proposed by Einstein when asked why there are more electrons than positrons in the universe: “The electrons got there first” – in other words, once both were in existence, each would start to annihilate the other until which ever had a slight excess would dominate our universe. More modern explanations of the excess of matter over anti-matter reflect the CPT (charge-parity-time symmetries) (Adair, 1988; Close, 2000a; Quinn & Witherell, 1998).

☞WWW☞ 6:25

Darwin talks about the warm pond in a letter to Joseph Hooker in 1871. Darwin continues by saying that “a protein compound was chemically formed, ready to undergo still more complex changes”, unlike in the present day when “such matter would be instantly devoured, or absorbed, which would not have been the case before living creatures were formed”.

The experiments of Miller on the early atmosphere are important and well known, not least because amino acids were produced in the test-tube simulations. What is essential to realise for present purposes is that the experiments only ever produced a 50:50 mixture of L and D forms. That point has been taken up by fundamentalist groups (e.g. www.yfiles.com/origin.html) to suggest it is evidence for an *ur*-biochemist: “The solution is simple, yet it has profound implications. To separate the two amino acid forms requires the introduction of *biochemical expertise* or *know-how*, which is the very antithesis of chance! However, biochemical expertise or know-how comes *only* from a mind” – the mind of God, in other words. Those criticism of the early experiments may well be valid, but they do of course ignore the subsequent half century or so of research.

Symmetry breaking in the possible conditions of the early earth continues to be a problem that excites many scientists, both physicists and chemists as well as biologists. As a result it is common for researchers to speculate that novel chiral mechanisms may be relevant to the origins of life on earth. An example is the finding that in some cases stirring a solution clockwise or anticlockwise can result in oppositely handed chiral products from reagents which are themselves achiral (Ribó et al., 2001). Although undoubtedly surprising and potentially of great interest for those trying to synthesise chiral pharmaceuticals and other chemicals, it is difficult to see how stirring could really be “a serious candidate for chiral selection in prebiotic stages of evolution” (Feringa, 2001) unless it is proposed that there were large consistently stirred pools of fluid on the early earth, which hardly seems likely, even given the existence of the Coriolis forces.

☞WWW☞ 6:27

It writing about physics, I am uncomfortably aware that I am a biological scientist by training, and my knowledge of physics, in particular particle physics, is that of an amateur. That is why I am not talking about the topic at length here. There are plenty of excellent books by those who do know what they are talking about, and anyone interested should look, for instance, at Martin Gardner’s classic *The ambidextrous universe* (1990b), or Frank Close’s more recent *Lucifer’s legacy* (2000a)

Wigner, a Hungarian physicist, who won the Nobel Prize in 1963, showed in 1927 that right-left symmetry and the conservation of parity are formally equivalent. For a selection of his writings see Wigner (1967).

Patrick Blackett (1897-1974) had himself been awarded the Nobel Prize for Physics in 1948, for his work on cloud chambers and its use for finding the positron.

The Wu experiment was actually a collaborative effort, and the usual convention of the time would have been to list the authors in alphabetical order, unless one author were the originator of the idea, when they should go first. Wu (1912-1997) was indeed the originator of the idea, but protocol was also that unless the originator suggested changing the order then alphabetical precedent should stand. Wu did not suggest it, and it would have been unseemly for the other authors to do so, and so the (male) authors suggested that Wu should appear first on the grounds that she was the only woman. As Kurti and Sutton (1997) comment, whether this is an early example of affirmative action or sexism is not clear. While on the topic, I have never been clear why Wu, a Professor at Columbia University in New York should so often be referred to as “Madam [or Madame] Wu”; that I suspect *is* sexism. For further background to the experiment see Hargittai and Hargittai (2000 pp.201-204).

As well as the Wu experiment on beta decay (Wu et al., 1957), there was also a second experiment on meson decay (Garwin, Lederman, & Weinrich, 1957) which also showed the same failure of conservation of parity, and within months there were dozens of others. Photographs of the original apparatus for the meson experiment can be found in Morrison (1957), including, amidst the vast piles of equipment, the key carbon block, “supported by a brick and coffee can”. Perhaps one of the most intriguing of the spin-offs from the parity experiments were the results, described Blackett in a 1958 lecture (1959 p.302) of a much earlier experiment, published in 1928, forty years previously, which had also shown that beta particles were not scattered equally to left and right (the rediscovery of the paper was made by Grodzins (Bernstein, 1962 p.88). The authors of that earlier experiment concluded that their results could come from “some asymmetry in the electron itself” (Cox, McIlwraith, & Kurrelmeyer, 1928 p.547), but since there was no theoretical framework for explaining the finding, the result was almost totally ignored: “I cannot remember ever having read or heard of Cox’s work”, as Blackett said, despite his close involvement with the field. Salam (1958) also pointed out that all the key evidence for the non-conservation of parity existed on photographic plates dating back at least a decade before the Wu experiment.

WWW 6:28

Yang called himself Frank after his hero, Benjamin Franklin, whereas Lee is known as “T.D.” (Regis, 1998 p.142).

Pauli, who won the Nobel Prize in 1945, is quoted by Salam (1958), who emphasises that ‘the *not* is heavily underscored’ by Pauli. Gleick (1994 p.334) emphasises how quickly, despite the strength with which the theoreticians had believed in parity, there was “a revisionists' purgatory in the making: theorists from Dirac to Gell-Man [were] 'busy explaining that they personally had never thought parity was anything special' ”.

☞ WWW ☞ 6:29

Almost immediately after the Wu experiment it was announced that μ mesons were even more strongly handed (Garwin, Lederman, & Weinrich, 1957). Subsequently it was found that all three types of neutrino are strongly left-handed, perhaps the most extreme example of failure of conservation of parity.

An electron is left-handed in precisely the same sense as a screw or a spiral is left-handed (Hegstrom & Kondepudi, 1990a). Imagine the electron rotating, like the earth around its north-south axis, and that the particle is itself also moving due north. A point on the surface of the particle will then form a left-handed helix and so the electron is left-handed, tracing out the same path as a left-handed corkscrew.

In a typical gambit from a theoretician, Pauli subsequently turned around completely the problem of failure of conservation of parity, and said, “I am shocked not by the fact that the Lord prefers the left hand as by the fact that he still appears to be left-handed symmetric when he expresses himself strongly. In short, the actual problem how seems to be the question: Why are strong interactions right-and-left symmetric?”(Gardner, 1990b p.218).

Bernstein (1962) gives an excellent in-depth journalistic account of the response of the world of physics to the stunning discovery. Within three months of the experiment, *Scientific American* had published a detailed account of it and its implications (Morrison, 1957).

Sadly it would seem that the Nobel Prize also split apart the very successful partnership of Lee and Yang, the relationship eventually foundering in part over that occasional but trivial source of intense irritation to scientists who collaborate on research papers – the order of names on the paper. This was apparently particularly intense for the *New Yorker* article (Bernstein, 1962), and one suspects the final title, “A question of parity” is deeply ironic. Eventually things deteriorated so much that Lee and Yang, or perhaps that should be Yang and Lee, each published books describing entirely different histories of their collaborative papers (Regis, 1998).

The precise extent of charge-parity violation is still controversial and problematic, a report in May 2001 estimating the key parameter particularly accurately and finding it to be outside the range expected by the standard model (Chen, 2001).

☞ WWW ☞ 6:30

Many years later Salam himself proposed a mechanism for the excess of L-amino acids which involved a Bose condensation at temperatures close to absolute zero, as might occur in the depths of space (Salam, 1991; Salam, 1992). However empirical testing suggests that the mechanism probably does not occur (Figureau, Duval, & Boukenter, 1995).

The quote about one-eye giants (Salam, 1958) is interesting, because as has been seen in a previous chapter, Dumézil (1974) had suggested that actually several early one-eyed heroes were indeed asymmetric.

There is a suggestion from a survey of 7563 galaxies that there is a 4.6% excess of left-handed galaxies (Mason, 1991 p.283). I have not however been able to trace this claim back to its source.

☞WWW☞ 6:31

Cline (1996 p.269) put it nicely: "Over the past 20 years, many experiments have been carried out [on the chemical effects of the weak interaction] ... However it appears that nearly every positive effect that was observed has turned out to be incorrect. In table 3 [of the Cline paper] we list some [few] experimental results that are not yet refuted or in direct conflict with previous null effects".

☞WWW☞ 6:32

The theory also explains something else which is otherwise rather mystifying. Although life is formed from L-amino acids it is made of D-sugars. Why is it not L-amino acids and L-sugars? The theory of the weak interaction neatly explains this, because although L-amino acids are more stable than D-amino acids, it is D-sugars which are more stable than L-sugars. So organisms are formed of the most stable amino acids and the most stable sugars (MacDermott, 1996 p.250). This is actually quite a triumph for the weak interaction theory since, as Bonner 1998b has pointed out, hardly any one has ever succeeded in explaining why there might be an excess of D-sugars.

☞WWW☞ 6:35

Although it is often presumed that the insides of meteorites must get very, very hot, there is evidence in at least one case that the interior may not even have been heated above 40°C (Weiss et al., 2000).

An account of the Murchison meteorite can be found in *The Times*, 30th September 1969, p.8h.

Other factors which exclude the possibility of contamination are that amino acids such as serine, threonine, tyrosine, phenylalanine, and methionine, which are common on earth, have not been detected in the Murchison meteorite (Engel & Nagy, 1982), and the proportions of the ¹³carbon and ¹⁵nitrogen isotopes are both higher than on Earth (Engel & Macko, 1997; Engel, Macko, & Silfer, 1990).

Several authors have quoted the early result on the 50:50 mixture of L- and D-amino acids and assumed that it means the meteoritic amino acids could not have come from contamination (Orgel, 1973, Gardner, 1990b). Interestingly, exactly the same argument was also used for the Murray meteorite, which fell in Kentucky on 20th September 1950 (Lawless et al., 1971), and was subsequently shown to have non-racemic mixtures of non-terrestrial amino acids (Pizzarello & Cronin, 2000).

The entire Tagish Lake meteorite is estimated as weighting about 200,000 kilograms. The fragments recovered are described as "lumps of crumbly rock with scorched, pitted surfaces - [they] resemble partly used charcoal briquettes: black, porous, fairly light and still smelling of sulfur" (www.space-science.com/headlines/y2000/ast16mar_1.htm). Early reports on its

chemical analyses suggest that the organic content is relatively low, and as yet there are no published reports on whether the amino acids are D- or L- (Hiroi, Zolensky, & Pieters, 2001, Pizzarello et al., 2001). A problem of analysing the meteorite seems to be that the owner has not yet parted with the relatively substantial samples which are needed for proper chemical analysis.

Although in this and the following sections I talk only of amino-acids as possibly having come from meteorites, it has also been demonstrated recently that the Murchison and Murray meteorites also contain sugar-related compounds that might also have had a role to play in initiating life on the early Earth (Cooper et al., 2001). As yet there seems to have been no analysis of whether the sugars are L- or D-, which would be of great interest.

☞ WWW ☞ 6:36

Curie's principle (1894) is the corollary of the statement by Francis Robert Japp in 1898, that "only asymmetry begets asymmetry" (Barrett et al., 1987).

For information on circularly polarized light see Bouchiat and Pottier (1984), and also accept.la.asu.edu/PiN/rdg/polarize/polarize.shtml. Despite the problems of replicating so many effects which claim to affect D- and L-amino acids differently, Cline (1996 p.269) says, "Th[e] observation that circularly polarised light destroys L and D isomers selectively ... is now well established ... and there is no doubt that this effect is real".

The most recent neutron star in our galaxy is the Crab pulsar, which exploded as a supernova on 4th July 1054 AD (Oort, 1957). The oldest supernova that we are aware of exploded about 20 million years ago. Within the Milky Way there are probably about 30,000 neutron stars which are sufficiently active to produce an enantiomeric excess in dust passing near by (within 1 parsec, about 3.25 light years) (Greenberg, 1996 p.201).

☞ WWW ☞ 6:37

This section is based strongly on the paper by Bonner (1998b). An important part of the evidence that amino acids in meteorites have indeed formed in the cold dark reaches of intergalactic space is provided by their high proportion of deuterium, an isotope of hydrogen (Epstein et al., 1987).

Although inter-galactic space is likely to be extremely cold, that does not necessarily mean that water is frozen into ice so hard that no chemical reactions can take place. So-called 'amorphous ice' can form in such conditions, and it has many of the properties of liquid water, and could well be a good place for organic compounds to form (Blake & Jenniskens, 2001).

☞ WWW ☞ 6:38

"Bucket loads" actually massively understates the amount of material that comets may have deposited on Earth. Halley's comet alone is one third organic material by mass, and about 3% of the organic material in carbonaceous chondrites is amino acids. In a paper of which Carl Sagan was a co-author (Chyba et al., 1990), it is estimated that between 10⁶ and 10⁷ kgms of organic material from impacting meteorites would have arrived on early Earth each year, of which about 1% would have been amino acids. To put this in perspective, the total mass of

biological material on Earth is about 6×10^{14} kgms, so that, even in the most extreme case, if *all* of this had come from meteorites it would have taken between 60 and 600 million years, very much less than the time that life has been on Earth.

On the problems of amino acids occurring spontaneously in the environment of the early Earth, Dyson (1999 p.17) points out that although Miller's classic experiments of 1953 synthesised amino acids in a simulation of the early atmosphere which was 'reducing', there is no evidence that the early atmosphere actually was reducing.

☞ WWW ☞ 6:39

Although Gould's argument is principally about the bacteria in the vernacular sense, it is clear from his evidence that it is a serious possibility that the archaea outweigh all other organisms on the planet (Gould, 1997).

☞ WWW ☞ 6:40

The idea that meteorites laden with L-amino acids were the origins of life on Earth is a nice one that is at least supported by the very solid evidence of large amounts of L-amino acids in meteorites. While there is no doubt that those meteorites do have the L-amino acids, there is rather more doubt about quite where they came from and why. The trouble with the theory of circularly polarised light is that circularly polarised light is not that common in the universe, although it can undoubtedly be found (and a recent report describes it in the Orion OMC-1 star-formation region (Bailey et al., 1998), and earlier work found polarised light around the Crab nebula (Oort, 1957)). An alternative possibility has been raised in a recent suggestion as to where homochirality came from. Pasteur himself, influenced by what it now seems was a complete misunderstanding of Faraday's work on the 'handedness' of magnetic fields, had thought that magnetic fields might induce crystals to grow one particular way (Barron, 2000; Lord Kelvin had however pointed out that "the magnetic rotation has neither left-handed nor right-handed quality, that is to say, no chirality"). A modern variant of the experiment has however worked, using what is known as the magnetochiral effect, in which light is adsorbed slightly differently by chiral molecules if the light is parallel to a magnetic field than if it is going in the opposite direction. The crucial thing about this is that the light does not have to be polarised – any old ordinary light will do. An experiment by Geert Rikken and Ernst Raupach (2000b), at the Max Planck Institute in Grenoble, found that when a racemic mixture of chiral molecules was placed in a strong magnetic field, with light going parallel to the field, then one enantiomorph of the chiral molecule tends to predominate. The effect is however small, only about one part in a thousand. Nevertheless it has much more scope for explaining the excess of L-amino acids than circularly polarised light, mainly because magnetic fields and light are everywhere, whereas circularly polarised light is rare. Having said that, the sort of magnetic fields found on earth seem too small to be able to produce the effect, particularly since most of the sunlight is at right angles to them, rather than parallel. It therefore seems probable, just as with the circularly polarised light theory, that the largest effects must be found in space, perhaps again near a neutron star.

The Hubble Space Telescope in October 1996 identified a neutron star relatively close to Earth. Although its precise distance is not known it lies in front of a molecular cloud about 400 light-years away, and hence must be closer than that. Its diameter has been estimated at 28 kilometres, and its extreme temperature (about $650,000^\circ\text{C}$) means it has to be a neutron star. It is not however a pulsar, emitting neither radio waves nor light, and so presumably is not rotating (www.seds.org/Maps/Const/Add/coronoaaustra_add.html).

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