Chirality

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# Tracing the Origins and Evolution of Chirality and Handedness in Chemical Language**

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chemical semiology · chirality · handedness · history of science · stereochemistry

*Dedicated to Ernest Eliel
and Kurt Mislow*

> “*Imagine … a musty storeroom crammed
> full of mannequin parts, left and right
> arms in rigidified plastic disarray
> And you, in the dark, have to sort
> them out. It's a left-over Fellini set
> It's soon done, but why
> is there one more right hand than left?*”
>
> Roald Hoffmann[1]

## 1. Introduction

The concept of chirality and the adjective chiral interest and inspire scientists worldwide. The discovery and study of chiral structures and morphologies, along with the asymmetry observed in natural phenomena and invented reactions, capture our imagination and provide further insights for cutting-edge research. Since controlling three-dimensional structure is a primary concern of many chemists, some have compared their work to that of artists.[2] And likewise some artists have been enticed by symmetry (or its lack) in their work. The Dutch engraver Maurits Escher (1898–1972) took admirable advantage of this visual language; his etchings *Drawing Hands* (Figure 1) and *Magic Mirror* are often portrayed in stereochemistry texts and websites.[3]

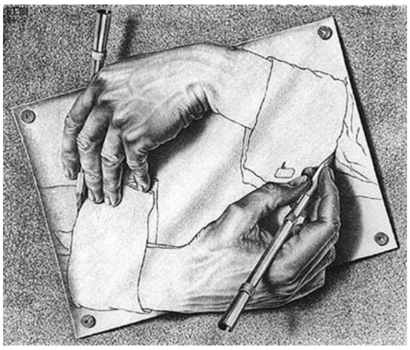

**Figure 1.** *Drawing Hands* by M. C. Escher.

But even though chirality, chiral, and related terms are scientifically appealing, there is considerable misuse and abuse of these expressions. Lord Kelvin formulated the concept of chirality more than one century ago, yet it took several decades before it became a key word in chemical textbooks. Moreover, the term chirality summarizes a long journey initiated not by scientists but by philosophers, mathematicians, and artists, who speculated on mirrors and their effects and eventually wondered about the reality of such inaccessible universes. This article briefly traces this never-ending story embracing chemistry and language, and describes how other disciplines, from physics to biology, have progressively incorporated chirality (and handedness or variations thereof) into their jargon, though the expression coexists with the more general and imprecise term of asymmetry.

## 2. Kant through the Looking-Glass

Since the 19th century, chemists have widely employed the term asymmetry, first in crystallography and later with molecular models. Because symmetry is a guiding principle in much of science,[4] its context is of prime importance. In chemistry, however, we are concerned chiefly with reflection symmetry,[5] which is relevant in both structure and synthesis.

Now a well-documented story, yet ignored by most chemists, the first epistemological discussion on handedness and its dependence on space's dimensionality begins with Immanuel Kant, the famous Prussian philosopher, who was captivated by what he dubbed incongruent counterparts to describe the existence of two nonsuperimposable mirror-image objects:[6] “*What can more resemble my hand or my ear, and be more equal in all points, than its image in the mirror? And yet I cannot put such a hand as is seen in the mirror in the place of its original …*”[*]

This Kantian analysis certainly fits in with our perception of identical and nonidentical objects, and that incongruent forms, exactly alike in all geometrical properties, are clearly not the same.[7] Although Kant had already anticipated geometries in spaces of higher dimensionality (his incongruent hands will actually become congruent objects in four-dimensional space), he concluded that space and time are a priori forms of human perception that shape and influence whatever is comprehended by our senses. Mirror-image

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[*] *“Was kann wohl meiner Hand oder meinem Ohr ähnlicher, und in allen Stücken gleicher sein, als ihr Bild im Spiegel? Und dennoch kann ich eine solche Hand, als im Spiegel gesehen wird, nicht an die Stelle ihres Urbildes setzen …”*

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solids in three-dimensional space are not things in themselves but phenomena based on our sensations and intuitions.[6] Nearly three centuries earlier, Leonardo formulated a related argument when he used mirror images as metaphors of his rivals:[8] "*Those who are inventors and interpreters between nature and man as compared with the reciters and trumpeters of the works of others, are to be considered simply as is an object in front of a mirror in comparison with its image when seen in the mirror, the one being something in itself, the other nothing*."

The above riddle was later extended by Lewis Carroll (pseudonym of Charles L. Dodgson), the English novelist, mathematician, and Oxford graduate, in *Through the Looking-Glass and What Alice Found There*, first published in December 1871,[9] which is probably the only nonscientific literature widely cited in the context of sterochemistry. In the dialogue between Alice and Humpty Dumpty, the philologist she found through the mirror, he asserts that "*a word means just what one chooses it to mean, neither more nor less*". Carroll assumes that it is all a matter of semantics and, not far from Kant's viewpoints, for two asymmetric, nonidentical objects, we cannot say which is which except when we introduce some characteristic feature that alters their relationships to each other in a given space.

English novelist and clergyman Edwin A. Abbott (1838–1926) explained in a metaphoric sense the puzzle for which Kant had thought he needed to invoke an ideal and subjective space. In *Flatland*,[10] a satire that appeared in 1884 against the highly hierarchical Victorian society, Abbott himself adopts the role of the narrator A. Square and guides the reader through a world in two dimensions (somewhat reminiscent of Alice's stories). A. Square dreams of a visit to Lineland (a one-dimensional world) and attempts to convince this kingdom's ignorant monarch of the existence of a second dimension. Square is then visited by a sphere, which he cannot understand until he sees the third dimension for himself. Abbott's tale has inspired modern mathematicians and physicists interested in higher dimensions and string theories.[11]

*Flatland* teaches us that two objects, such as the scalene triangle or an oriented circle, may not be identical or enantiomorphous. The fantastic stories written by Abbott were preceded by a more rigorous mathematical study: August F. Möbius (1790–1868), for whom the Möbius strip is named, proved that two nonsuperimposable objects in three-dimensional space become identical when one of them is rotated (in other words, turned over) in a fourth, though physically unattainable, dimension.[12] Accordingly, enantiomorphous images obtained by reflection in $n$-dimensional space are actually homomorphous (or completely congruent) by rotation in an $(n+1)$th dimension.

The American mathematician Martin Gardner offered an additional tour de force on handedness, the so-called Ozma problem: How can two intelligent civilizations agree on the description of an asymmetric object as left- or right-handed without a prior understanding of such terms?[13] In fact, they cannot unless we are able to introduce the concept of handedness as universal and constant, such as parity violation, together with a detectable parameter of its manifestation.[14]

At the molecular level, chemists describe the sense of handedness (or configuration) relative to a reference conventionally accepted (for instance, clockwise or anticlockwise) that then differentiates two enantiomorphous objects. Examples include the CIP system of nomenclature for rigid molecules,[15] the descriptors assigned to topological objects,[16] and human laterality (see Section 6), in which the position of the heart is arbitrarily defined as left.

## 3. Pasteur and Dissymmetry

This linguistic and conceptual dissection cannot overlook Pasteur, who anticipated molecular asymmetry in his crystallographic studies. Pasteur's great achievement of 1848, the mechanical separation of tartrate enantiomers, was a milestone in the search for the origin of optical activity in crystals, a topic that had attracted a plethora of scientists since the beginning of the 19th century.[17] Instrumental figures were Pasteur's mentor, Biot (whose actual role has largely been overlooked),[18] and Herschel,[19] the British astronomer who noted a correlation between optical rotation and crystal hemihedrism (the fact that crystals such as quartz exhibit facets arranged as to produce nonsuperimposable mirror images).

The rest of this chapter of stereochemistry is quite well known.[20] Taking advantage of the hemihedrism of tartrate crystals, which is not usually observed for crystals of optically active substances with facets inclining to the right or left, Pasteur was able to achieve the first resolution (levorotatory tartaric acid was unknown up to that time). On dissolving the two kinds of crystals separately, he determined their optical activity to be identical and of opposite sign. Pasteur was in the position to provide a satisfactory rationale of this and previous experiments,[18] by extending the concept of hemihedric faces observed in crystals to the realm of molecules in solution: "*I consider as extremely probable that the mysterious, unknown disposition of physical molecules in a whole and finite quartz crystal is found in (optically) active bodies, but, this time, in each molecule taken in particular.*"[*][21] He then coined the term *dissymétrie moléculaire* (molecular dissymmetry) to describe the structural arrangement found in quartz, which he extrapolated to tartrate molecules:[22] "*Tartaric acid and its combinations have all dissymmetric forms … All of these tartrate forms have individually a nonsuperimposable mirror image … the dissymmetry of the tartrate form correlates with its optical dissymmetry.*"[**]

Some stereochemists argue that Pasteur's dissymmetry (like Kant's incongruent counterparts) translates well today as chirality or handedness (Section 4), because it contains the essence of enantiomorphism, that is, nonsuperimposable mirror images.[16] However,

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[*] *"Je regarde comme extrêmement probable que la disposition mystérieuse, inconnue, des molécules physiques, dans un cristal entier et fini de quartz, se retrouve dans les corps actifs, mais, cette fois, dans chaque molécule prise en particulier."*

[**] *"L'acide tartrique et toutes ses combinaisons ont des formes dissymétriques … Toutes ces formes tartriques ont individuellement une image dans la glace qui ne leur (est) pas superposable … la dissymétrie de la forme du tartrate correspondra à sa dissymétrie optique."*

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historians of stereochemistry point out that Pasteur did not think of molecules in terms of the then-emerging structure theory, which was really a pity. In his mind, dissymmetric molecules could be thought of as arrangements of atoms in geometries capable of generating non-imsuperposable images like spiral stairs or even a collection of tetrahedra![23] Pasteur's inattention to the theory of valency and the problem of stereoisomerism in general prevented him from obtaining the final solution.[24] For instance, he did not attempt the resolution of malic acid as its crystals do not exhibit hemihedrism. This suggests that, to a significant extent, Pasteur associated dissymmetry at a molecular level to what he macroscopically observed in crystalline forms.

At this stage it is appropriate to recreate a little bit the historical development of organic chemistry around 1874 (obviously this cannot be detailed here and the reader is referred to, among others, a recent monograph by Ramberg).[25] Prior to this annus mirabilis, organic chemistry had experienced a quiet revolution and had progressed from a branch of natural history to an experimental science based on a growing number of synthetic compounds and the emergence of the structure theory during the 1860s. Structural formulas were initially intended to be a symbolic representation.[26,27] Van't Hoff's introduction of a physical geometry for the carbon atom radically changed the way chemists viewed chemical formulas, and a conventional symbolic language was transformed into an iconic language. It is worth pointing out that the spatial notation did not replace the significance of structural formulas but simply added another layer of understanding. Wislicenus, to a certain extent van't Hoff's most adament proponent, declared by the 1890s that it was impossible not to conceive of atoms as three-dimensional objects.[28] As a result, formulas now contained hypothetico-deductive understanding that enabled chemists to make theoretical predictions.

Although Pasteur was the first to show a relationship between optical activity and dissymmetry at the molecular level, he could not say exactly how a molecule could be right- or left-handed. This does not diminish Pasteur's merit. Buckingham recalls that what counts most is not the individual genius as much as the intellectual climate and practical environment that allows the merely talented to florish and contribute to each other's success.[29]

By the end of the 19th century, in further discussions on Pasteur's discovery and its implications, the term dissymmetry was progressively replaced by the term asymmetry.[30] Remarkably, dissymmetry, now obsolete and discouraged in modern stereochemistry nomenclature, survived in pioneering textbooks (see below) as a semantic distinction between two kinds of optically active substances.[31]

One cannot conclude Pasteur's story without returning to Lewis Carroll. The most invoked sentence extracted from *Through the Looking-Glass*, which is often quoted in scientific papers on asymmetric synthesis and stereochemistry, is what Alice said to her cat: “*How would you like to live in a looking-glass house, Kitty? … Perhaps looking-glass milk isn't good to drink.*” Carroll would hardly have been aware of what this question implies as he was ignorant of the chemical and stereochemical composition of milk.[32] Alice's question seems to be a literary clue as Carroll's illusory world behind the mirror does not actually reflect the real world and, therefore one can imagine anomalous properties and behavior in facts and substances. However, in one anecdote, it is also said that a colleague of Carroll from the University of Oxford, trained in chemistry and well-acquainted with Pasteur's experiments, such as his manual separation of tartrate enantiomers (1848) and notably that only the right-handed enantiomer underwent yeast fermentation (1857), would have referred Carroll to such discoveries (*Through the Looking-Glass* appeared in 1871). That mirrored milk might have modified physiological effects would not be so foolish after all.

## 4. Kelvin's Concept: Why So Late?

It is not necessary to emphasize the importance of the concept of chirality; one only has to look at any leading journal to realize how much research is conducted related to this key word. What is, however, less known to most practitioners is the origin and further evolution of the term chiral (from Greek *kheir*: hand) in the famous quotation from Kelvin: “*I call any geometrical figure or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself. 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.*”

The source of this quote and of the term chiral itself is obscure and cannot be traced with complete accuracy. This story has been documented in more detail by Mislow in his excellent account on molecular chirality.[16] In short, the definition was included in an appendix of Kelvin's Baltimore lectures delivered in 1884 but not published until 1904.[33] In this series of talks at Johns Hopkins University, William Thomson, Lord Kelvin, (Figure 2) addressed the state of scientific knowledge and hypothesized on the failures of the wave theory of light to explain certain phenomena.[34]

Apparently the term chiral was never used in the Baltimore lectures but

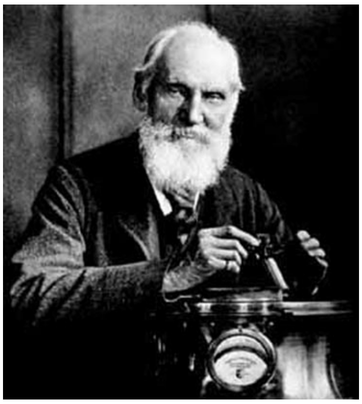

**Figure 2.** William Thomson (1824–1907), knighted in 1866 by Queen Victoria for his work and elevated to Baron Kelvin of Largs in 1892. He caught the essence of enantiomorphism in the concept of chirality, which was published as a marginal footnote. Kelvin would hardly have realized how captivating this concept really is.

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added at the time of publication, presumably by Kelvin himself who died in 1907. Kelvin's coinage of such Greek-based terms should be dated earlier, to at least 1873 when he gave a lecture, whose text was never published, at the Royal Society of Edinburgh: "*Note on Homocheiral and Heterocheiral Similarity*".[16] (It is noteworthy that these terms derive strictly from the Greek word *kheir.*) Remarkably, another Scottish physicist and mathematician, Peter Guthrie Tait (1831–1901), professor of natural philosophy at the University of Edinburgh from 1860 and with whom Kelvin had collaborated,[35] picked up the term *cheiral*. Tait dealt with some fundamental problems in knot theory, such as *cheirality* and crossing number, and introduced the graph of a knot. The term amphicheiral (from *amphi*: on both sides + *kheir*: hand) coined around that time, means topologically achiral.[36]

With *cheirality* (and later chirality) confined to algebraic and topological problems, it is not difficult to understand why chemists ignored the term for nearly one century. But topological chirality clearly deviates from Kelvin's definition, which applies to nondeformable, isometric species (an object is topologically chiral if, and only, if it cannot be converted into its mirror image by continuous deformation in a given *n*-dimensional space).[37]

In the early 1980s when I was completing my undergraduate studies, I had an inspiring organic chemistry teacher who recommended that I read Eliel's book *Stereochemistry of Carbon Compounds*, first published in 1962.[31] I was fascinated by this topic and decided to pursue a research career with a focus on stereochemistry. This textbook actually filled a void in organic chemistry and had a major influence on many chemists. At the time of the first publishing of Eliel's book only some textbooks in German and a few specialized chapters in English books dealing with stereochemistry had been published.[38,39] Already familiar with the concept of chirality, I was baffled to see the omission of the term in Eliel's book, though it drew attention to molecular dissymmetry. It was Mislow in his *Introduction to Stereochemistry* (a text initially discouraged by my mentor as reading suitable for a beginner),[40] who rescued the term chirality for future generations of students and teachers. In Mislow's words (what a wonderful sentence, plenty of stereochemical synonyms!): "*The screw sense (right or left) which characterizes a given dissymmetric conformation or helix is the* chirality, *a term which may be applied to any dissymmetric object or molecule and which refers to the handedness of a given enantiomeric form.*"

It is fair to say that Lancelot Whyte (1896–1972) had previously vindicated the term chiral in two letters that appeared in *Nature* both entitled "Chirality".[41]

Kelvin's definition also echoes the Kantian dissertation on incongruent counterparts. Not surprisingly, Prelog unified both arguments in a modern definition that equally considers what would otherwise be allowed to make both objects identical in the Euclidean space, that is, rigid rotations and translations.[42] However, chemists devoted to topological structures have long struggled to accommodate language to thought models. It is therefore necessary to consider the actual relations between those models and the physical phenomena they are intended to represent. This question has a practical relevance because natural products such as polypeptides or nucleic acids, together with sophisticated synthetic molecules, are topologically chiral.[37,43,44]

A chemical molecule can be represented by a mathematical structure, a graph, which is no more than a discrete collection of vertices joined by edges. Graphs embedded in a plane without the intersection of any edges are denoted planar graphs, otherwise they are nonplanar. In the case of conventional chiral molecules, let us say, one with a tetrahedral carbon attached to four different ligands, its graph is a planar representation with all vertices in a plane. The latter is stereochemically unrealistic but topologically equivalent to the former. (We only need a geometry representing a realistic constitution.) For large and flexible molecules the situation is different, and this raises the question: could it be possible to deform the graph to the shape of its mirror image? A graph that cannot be continuously deformed to its mirror image is said to be topologically chiral. But in topology, all possible deformations of a given graph are taken into account, and not all such deformations need to be realizable for an actual molecule; in other words, either the right-hand or the left-hand side could be inaccessible to the experiment.

Flapan points out that topological chirality and chemical chirality need not be the same.[37] A chemist, not a mathematician, might find this sentence disconcerting because, after all, molecules with a flexible shape such as a trefoil knot can be synthesized and resolved into its enantiomers, thus giving proof of chirality. Does this chirality disagree with Kelvin's concept, or does the image create the concept?

Leaving aside that real molecules are time-averaged structures and not a static collection of points, Mislow reasonably adds that the symmetry of a model of a molecule depends on the conditions of its physical or chemical measurement. Hence, the chirality or achiraliy of the model depends on the conditions of observation.[45] While the topological chirality or achirality of a molecule refers exclusively to its molecular graph, we can get further insight by going back to the presentation of images as readable signs,[46] something essential in modern biological sciences.

Consider, for instance, a micrograph of a cardiac cell. One can distinguish, among several substructures, the mitochondria of the cell which are sometimes oval, sometimes curved (Figure 3). They are variable but within the same order of magnitude, and their texture is characteristic and different from that of their environment. With a large collec-

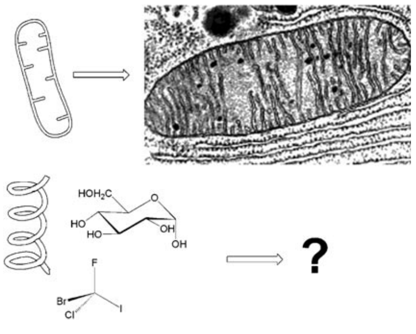

**Figure 3.** Linguistic or visual puzzles: how real are molecular (topological and non-topological) objects? Formal representations (bottom) include layers of knowledge, just like the over-reductionism of a (real) mitochondrion (top).

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tion of micrographs such data are suitable for computational analysis. The data can be reduced to quantitative measurements and summarized in statements in the form of a theory. The patterns appearing in such representations should exhibit invariances with respect to the similarity groups and are characterized topologically by their connection types. Thus, theoretical concepts are a formal representation of knowledge.[47] In Kelvin's words chirality appears as a mathematical analogy, in which the terms "object" and "ideally realized" have a geometrical value and are not intended to describe a physical phenomenon. This is also what one might expect from a scientist with an exceptional training in mathematics but little or no contact with the structural theories of his time.

In the late 1980s stereochemists saw a further assault on Kelvin's definition when Laurence Barron, in an attempt to extend the notion of chirality to the submolecular world as well as to fields that can be represented by scalar or vectorial magnitudes, introduced the concepts of true and false chirality:[48] "*True chirality is exhibited by systems that exist in two enantiomorphic states that are interconverted by space inversion, but not by time reversal combined with any proper spatial rotation.*"

At first glance, and with the sole exception of spatial rotation, this definition has little to do with the classical definition of chirality provided by Kelvin. As we shall see later, this inconsistency is apparent because, as mentioned, the hallmark of chirality is the incongruence of two mirror images, no matter how the nonequivalence can be realized. Barron borrows from physics the so-called discrete symmetries such as space inversion (or parity, P) and time reversal (T), which characterize the physical laws, thereby going to more fundamental operations. This has often led to a muddle, even though the notion of, for instance, parity violation has become increasingly popular, and practitioners have incorporated it into their language. However, a few linguistic barriers often impede chemists' quick comprehension:

1) Space inversion is not the same as mirror reflection; the former sends a system with $(x,y,z)$ coordinates in front of the mirror to an idealized image with $(-x,-y,-z)$ coordinates, whereas for mirror reflection an object occupying the $y,z$ plane will have an image with $(-x,y,z)$ coordinates behind the mirror. If one considers a stationary object, a finite helix, for example, the result is equivalent: reflection followed by a rotation through 180° about an axis perpendicular to the reflection plane.
2) Obviously, time reversal (i.e. every motion would reverse its direction) is irrelevant. But if motion is a key aspect, the enantiomorphism to be observed in a given space should be time invariant. Accordingly, T is a geometry operation for a truly chiral system, while for a falsely chiral one neither P nor T are symmetry operations but the combination of P and T.[48c]

Although the assignment of true and false enantiomorphism is not always unanimous,[16] and "true" and "false" have strong dialectic connotations, a reinterpretation of Kelvin's statement considering a spatio-temporal background provides, to a certain extent, the hidden elements of mirror reflection that Kant was long looking for.

The P/T reformulation moves chirality—if we may say so—from the benchtop to the microscope. Thus we can appreciate subtle remarks such as the fact that achirality per se does not really exist, given the parity violation in matter. As to whether a particular molecule or object may be chiral or achiral, the answer is context dependent. This may engender the view that some contradictions are true, a view that runs against logic that philosophers call dialetheism.[49] We need, however, a certain vagueness, which is a characteristic of human language, inherent to the physical world we find ourselves in, and subsequently inherent to any attempt to communicate features of it to each other. Perhaps, John Polanyi said it best: "*Scientia is knowledge. It is only in the popular mind that it is equated with facts.*"[50]

## 5. What Is Chiral and What Is Not?

With the impressive development of asymmetric synthesis, we inevitably associate chiral and chirality with reactions and processes. In their authoritative treatise on stereochemistry, Eliel and Wilen alert on the proper use:[51] "*[The] use of the word chiral should be restricted to molecules (or models thereof) and substances as in chiral substrate, chiral catalyst, chiral stationary phase, and so on. However, we strongly discourage the application of the word to processes, as in chiral synthesis, chiral catalysis, chiral recognition, chiral chromatography, and so on.*"

One can certainly designate a transformation as asymmetric because it selectively follows one path.[52,53] Eliel and Wilen emphasize again the geometrical character of chirality when they discuss the topic of stereoisomer discrimination (both enantiomer and diastereomer discrimination),[54] a concept we often misuse as chiral discrimination and/or chiral recognition: "*We prefer the term stereoisomer discrimination to the more widely used expression* chiral discrimination *(or chiral recognition) to emphasize its nature. There is nothing chiral about the discrimination per se; and while it is exhibited by chiral substances, it is caused by diastereomer, not enantiomer differences.*"

The latter part of this quote is particularly timely as Mislow recalls the differences between enantiomers and diastereomers. The relationship between enantiomers is established by symmetry alone and does not require any knowledge of constitution. In contrast, diastereomers are not related by symmetry, and their relationship can be defined only by first specifying that their constitutions are the same. Diastereomers have more in common with constitutional isomers than with enantiomers.[55]

One can go further to designate the sense of chirality and to assign a homochiral class, that is, one in which all the objects have the same handedness or configuration. As strange as it may seem, chirality and handedness are not perfect synonyms. If a molecule is chiral, it must be either right-handed or left-handed. With a collection of chiral

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molecules or chiral objects, there is an obvious distribution of these species between two subsets. If the chiral objects are, say, all shoes, two subsets denoted conventionally left and right shoes are readily generated, both of which are a homochiral class regardless of whether the shoes differ in other features such as shape, size, or color. But this situation is not immediate with other chiral objects such as potatoes. The description of any potato that is neither identical to nor the mirror image of a potato already in a subset requires an extra guiding principle. Left- or right-handed is meaningless for potatoes, even if they are generally chiral (or in other words, it would be extremely difficult to identify the opposite handedness in the same way one does with shoes).

Chiral molecules with a tetrahedral skeleton bearing four nonequivalent ligands can be considered shoelike objects, while for some chiral molecules with other polyhedral skeleta the unambiguous dissection into homochiral classes is not easily feasible (potatolike objects).[56] A thought-provoking conclusion is that all handed objects are chiral, but not all chiral objects are handed.[56b] Handedness is thus related to the possibility of classifying chiral objects as right-handed or left-handed. Nonhanded chiral objects are analogous to potatoes, which have no symmetry because of their irregular shapes, thereby meeting the requirements for chirality.

Although it is not easy to translate these ideas relying on chirality algebra into more prosaic language, Mezey argues clearly that a natural separation of homochiral classes is provided by the achiral structures.[57] For chiral tetrahedral molecules any deformation of a member of a homochiral class will result in an achiral intermediate before the mirror-image structure is obtained that belongs to the other homochiral class. However, for other chiral skeletons, there will be deformation paths interconverting the two mirror images along which all arrangements are chiral. Thus, it is not obvious which structures along the path should be considered to belong to a particular homochiral class. The geometrical definition of homochirality leads to ambiguity. It is somewhat ironic that 19th century chemists did not show an initial interest in the optical activity of octahedral complexes, nor did they expect spontaneous resolution of these substances.[58]

## 6. Coda: Chemistry and Beyond

The notion of chirality has become a fundamental concept that concerns chemists to a significant extent, and asymmetry gives physicists some trouble when they try to explain why our world is not symmetric under certain operations. Although particle phenomena may not have a direct relationship with molecular behavior, has been recognized in condensed-matter physics that quantitative measures of phase transitions and mathematical modeling may have practical applications in chemistry. Up until recently, chirality was a rather unusual term among physicists, especially because symmetry violations may be conceptualized under different terms (see below). Its increased use is exemplified in a tutorial commentary on the handedness of quarks by Nobelist Frank Wilczek: "*If the spin axis is aligned with the direction of motion, then the sense of the rotation defines a handedness, known as chirality. The two possible states of chirality of a quark, left and right, are essentially the same concept as left and right circular polarization of photons.*"[59]

Conversely, chemistry has gained a deeper insight into how phase transitions occur (from racemic to chiral states) and sound explanations on, for instance, the behavior of noncentrosymmetric materials. But both areas are still far from sharing a common language. As noted by some authors, one should be particularly cautious with the concept of symmetry breaking[60] and, above all, avoid the use of the term chiral symmetry[61] because chemists and physicists generally understand different things. As suggested by Walba,[53a] the terms reflection symmetry breaking or mirror-image symmetry breaking (which most chemists really detect in resolutions and stereoselective reactions) are clearly understood. Alternatively, the term mirror asymmetry often used by physicists[62] appears to be in line with chirality.

But arguably, the major connection between asymmetry and life is related to animal embryogenesis (this is indeed biochirality).[63] Paleobiologists employ in this context the term symmetry breaking to denote the morphological evolution and phylogenetic position of species with various symmetry types: spherical, radial, and bilateral.[64] These symmetries can further be broken into chiral and pseudo-bilateral forms, the latter resulting from the nonequivalent placement of some internal organs or the unequal development of paired organs. It is noteworthy that laterality is the term that replaces handedness in biology and psychology to denote leftward or rightward biases.[65]

One could come up with possible evolutionary arguments for why organisms display laterality (optimal packing during development, etc.); there is, however, no plausible reason why organisms should all be asymmetric in the same sense. A remarkable, though rare, case of natural enantiomorphism occurs in animals with complete mirror reversal of internal organs (*situs inversus*), which are otherwise phenotypically unimpaired.[64c] The condition of *situs inversus* was initially reported as *heterotaxy* by English physician T. Watson after he had examined an individual with the heart on the right side. Surprisingly, this patient was right-handed.[66] Since most people are right-handed and have their heart on the left side, one could expect left-handedness in individuals with *situs inversus*. Modern research in biology and psychology reveals that this assumption is often wrong and, remarkably, it extends the concept of laterality beyond the traditional views of handedness and chirality.

There is of course much more that can be described in terms related to chemists' chirality and handedness. Escher can provide the epilogue. Figure 4 shows his version of the renowned topological object, the Möbius strip. Like in the Greek myth of Sisyphus, the ants are punished by having to crawl unceasingly on a nonoriented two-dimensional object, thereby giving an idea of infinity. Perhaps the authors of the first Möbius annulenes were inspired by Escher's work, as they illustrated the cover of a recent issue of *Chemistry—A*

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*Figure 4.* Möbius Band II by M. C. Escher.

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Concept
Organocatalysis Mediated by
(Thio)urea Derivatives
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*Figure 5.* Escher's touch decorating Moebius annulenes.

*European Journal* (Figure 5) with a closely related design.[67]

Our natural world is filled with structural motifs that reveal an intrinsic handedness[68] and the cognitive apprehension of their nonidentity when viewed "behind the looking glass". Whether or not such objects exist, in worlds that may be either possible or impossible, they always offer visual and linguistic challenges and a link between science and art that will never be disappointing.

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[1] R. Hoffmann, *Catalista. Selected Poems*, Huerga & Fierro, Madrid, **2002**, p. 64 (bilingual book with the Spanish translation by F. García Olmedo).

[2] R. Root-Bernstein, *HYLE* **2003**, *9*, 35–53.

[3] D. Schattschneider, *M. C. Escher: Visions of Symmetry*, Harry N. Abrams, New York, **2004**. Escher repeatedly visited the Alhambra, the Moorish palace of Granada, where he was inspired by the splendid arabesques featuring order and symmetry. A mathematical study of such ornamentations has revealed that they exactly match the 17 plane groups possible for all two-dimensional patterns: A. F. Costa González, B. Gómez García, *Arabescos y Geometría (Video Tape)*, UNED, Madrid, **1995**.

[4] J. Sivardière, *La Symétrie en Mathématiques, Physique et Chimie*, Presses Universitaires de Grenoble, **1995**.

[5] In chemistry, we often refer to left–right symmetry (or left-handed/right-handed forms) in an attempt to convey exactly what a mirror does. That is, conventional mirrors reverse only the left and right sides of things, but not up and down. From a mathematical viewpoint this assumption is also wrong: The mirror does not reverse left and right at all, it reverses front and back! This is simply a result of a bilateral symmetry (common not only to humans but also to other animals and objects), meaning that the left side is a mirror reflection of the right. When one moves the right hand, one sees that the mirror image moves its left hand. Thus, left–right reversal is the convenient terminology we have developed to distinguish a bilaterally symmetric object from its enantiomorph. Perhaps, the great physicist Richard Feynman described the concept most clearly: "*It is the same with a book. If the letters are reversed left and right in a mirror, it is because we turned the book about a vertical axis to face the mirror. We could just as easily turn the book from bottom to top instead, in which case the letters will appear upside down.*" (J. Gleick, *Genius: Richard Feynman and Modern Physics*, Abacus, London, **1994**, p. 331).

[6] I. Kant, *Prolegomena zu einer jeden künftigen Metaphysik die als Wissenschaft wird auftreten können*, **1783**. For an English translation see: *Immanuel Kant's Prolegomena to Any Future Metaphysics* (Ed.: B. Logan), Routledge, London, **1996**. Full contents of *Prolegomena* in English are also available online: http://philosophy.eserver.org/kant-prolegomena.txt (see First Part, Section 12).

[7] R. Hoffmann, *The Same and Not the Same*, Columbia University Press, New York, **1995**.

[8] E. MacCurdy, *Leonardo da Vinci's Notebooks Arranged and Rendered into English*, *Vol. 1*, Jonathan Cape, London, **1938**, p. 61.

[9] The book was, however, dated 1872 and published by Macmillan, London, the same publishing house that had published *Alice's Adventures in Wonderland* in 1864. Both books were illustrated by John Tenniel.

[10] E. A. Abbott, *Flatland—A Romance of Many Dimensions*, Dover Publications, **1956** (reprinted from the 6th edition).

[11] a) I. Stewart, *The Annotated Flatland: A Romance of Many Dimensions*, Basic Books, New York, **2001**; b) I. Stewart, *Flatterland: Like Flatland, Only More So*, Basic Books, New York, **2002**.

[12] A. F. Möbius, *Der barycentrische Calcul* (*The Calculus of Centers of Gravity*), J. Ambrosius Barth Verlag, Leipzig, **1827**.

[13] M. Gardner, *The New Ambidextrous Universe*, 3rd ed., W. H. Freeman, New York, **1990**, Chap. 18, pp. 165–171.

[14] The problem has been addressed repeatedly, also by R. Feynman prior to Gardner's hypothesis: *The Feynman Lectures on Physics*, *Vol. 1*, Addison-Wesley, Reading, MA, **1965**, Chap. 52. Recent thought experiments point to a reliable solution of the Ozma problem by showing that parity violation modifies sum-frequency generation that would then distinguish two different configurations: N. Ji, R. A. Harris, *J. Phys. Chem. B* **2006**, *110*, 18744–18747.

[15] S. R. Buxton, S. M. Roberts, *Guide to Organic Stereochemistry*, Prentice Hall, **1996**, Chaps. 2–4, pp. 25–59.

[16] K. Mislow, *Top. Stereochem.* **1999**, *22*, 1–82.

[17] J. Rosmorduc, *Bull. Union Physiciens* **1984**, *667*, 85–99, and references therein.

[18] A long-held, erroneous idea is that Pasteur discovered the optical activity of tartaric acid. This phenomenon was first observed by Jean-Baptiste Biot (1774–1862), who pursued studies on polarimetry from 1812 until his death. Biot recognized that rotation of polarized light by quartz is an inherent property of the crystal ("Mémoire sur un nouveau genre d'oscillation que les molécules de lumière éprouvent en traversant certains cristaux": J.-B. Biot, *Mem. Inst.* **1812**, *13*, 1–371; for dextro- and levorotatory quartz, pp. 262–263), while this behavior of some natural liquids or solutions of solids (oil of turpentine, oil of lemon, camphor in alcohol, sugar in water) seems to be a property of individual molecules ("Phénomènes de polarisation successive, ob-

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servés dans les fluides homogènes": J.-B. Biot, *Bull. Soc. Philomath. Paris* **1815**, 190–192). Later, he advanced a "molecular" explanation, although the term molecule by that time should be interpreted in a broad, flexible sense, related to Newton's corpuscular theory: "*the phenomenon] being a property of molecules regardless of their state of aggregation*" ("*… une faculté propre à ces molécules indépendamment de leur état d'agrégation*"; "Mémoire sur les rotations que certaines substances impriment aux axes de polarisation des rayons lumineux": J.-B. Biot, *Mem. Acad. Sci. Inst. Fr.* **1817**, *2*, 41–136).

[19] J. F. W. Herschel, *Cambridge Phil. Soc. Trans. I* **1822**, 43–52.

[20] P. Ball, *Elegant Solutions. Ten Beautiful Experiments in Chemistry*, Royal Society of Chemistry, Cambridge, **2005**, pp. 101–118. This remarkable discovery has been described in later hagiographies of Pasteur with a certain eureka-like style, but it probably did not occur in the same way.

[21] L. Pasteur, *Œuvres de Pasteur*, *Vol. 1*, Masson, Paris, **1922**, p. 21 (La dissymétrie moléculaire).

[22] Extracted from a conference given by Pasteur at the Société Chimique de Paris on Dec. 22, **1883**. See also L. Pasteur, *Œuvres de Pasteur*, *Vol. 1*, Masson, Paris, **1922**, pp. 370–372.

[23] See L. Pasteur, *Œuvres de Pasteur*, *Vol. 1*, Masson, Paris, **1922**, p. 329, 372–374.

[24] O. B. Ramsay, *Stereochemistry*, Heyden, London, **1981**, Chap. 4, pp. 72–78.

[25] P. J. Ramberg, *Chemical Structure, Spatial Arrangement. The Early History of Stereochemistry, 1874–1914*, Ashgate, Burlington, VT, **2003**.

[26] See O. B. Ramsay, *Stereochemistry*, Heyden, London, **1981**, Chap. 5, pp. 92–94.

[27] P. Cintas, *Found. Chem.* **2002**, *4*, 149–161.

[28] P. Ramberg, *Bull. Hist. Chem.* **1994**, *15/16*, 45–53.

[29] J. Buckingham, *Chasing the Molecule*, Sutton Publishing, **2004**, pp. 75–76 plus Chap. 14.

[30] For instance, in 1898 *Nature* published a series of letters in response to a previous article by F. R. Japp entitled "Stereochemistry and Vitalism" that summarized Pasteur's work and refers to asymmetric molecules and asymmetry. A detailed analysis of this correspondence can be found in M. Gardner, *The New Ambidextrous Universe*, 3rd ed., W. H. Freeman, New York, **1990**, pp. 141, 144.

[31] E. L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**, pp. 9–10: "*An asymmetric molecule lacks both simple and alternating axes of symmetry, whereas a dissymmetric molecule lacks an alternating axis of symmetry (it may or may not be asymmetric).*"

[32] By the late 1860s it was known that lactic acid from sour milk was optically inactive, while the so-called sarcolactic acid from muscle tissue, which has similar properties, was optically active. No chemical resolution of milk lactic acid was attempted, and therefore it was never determined whether an enantiomer of sarcolactic acid might be present in milk. See O. B. Ramsay, *Stereochemistry*, Heyden, London, **1981**, pp. 78–80.

[33] W. Thomson Kelvin, *Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light*, C. J. Clay, London, **1904**.

[34] H. I. Sharlin, *The New Encyclopaedia Britannica*, *Vol. 22*, 15th ed., Encyclopaedia Britannica, Chicago, IL, **1990**, pp. 503–505.

[35] The two scientists produced the *Treatise on Natural Philosophy* (1867), which traced the concept of conservation of energy to the work of Isaac Newton, and had a major influence on future physicists. *The Elements of Natural Philosophy*, also coauthored by Kelvin and Tait appeared in 1872.

[36] *Amphicheiral* knots (i.e. their enantiomorphous presentations can be interconverted by continuous deformation) had been described previously by the German mathematician J. B. Listing, who recognized that trefoil knots exist in two nonidentical mirror images, see Ref. [16].

[37] E. Flapan, *When Topology Meets Chemistry. A Topological Look at Molecular Chirality*, Cambridge University Press, Cambridge, **2000**.

[38] a) R. L. Shriner, R. Adams, C. S. Marvel in *Organic Chemistry*, *Vol. I*, 2nd ed. (Ed.: H. Gilman), Wiley, New York, **1943**, Chap. 4; b) The first volume of *Progress in Stereochemistry*, edited by W. Klyne and published by Academic Press, appeared in 1954; Vol. II (1958) and Vol. III (1962) were coedited by W. Klyne and P. B. D. De La Mare.

[39] For a historical perspective: E. L. Eliel, *Abstracts of Papers*, 230th National Meeting of the American Chemical Society, Washington, DC, **2005**, HIST9.

[40] K. Mislow, *Introduction to Stereochemistry*, Benjamin, Reading, MA, **1965**, pp. 51–52.

[41] a) L. L. Whyte, *Nature* **1957**, *180*, 513; b) L. L. Whyte, *Nature* **1958**, *182*, 198; c) there is also an interesting posthumous paper: *Leonardo* **1975**, *8*, 245–248.

[42] "*An object is chiral if it cannot be brought into congruence with its mirror image by translation and rotation. Such objects are devoid of symmetry elements which include reflection: mirror planes, inversion centers, or improper rotational axes*": V. Prelog, *J. Mol. Catal.* **1975/76**, *1*, 159–172 (Nobel lecture).

[43] D. M. Walba, *Tetrahedron* **1985**, *41*, 3161–3212.

[44] Chiral borromeates have been prepared recently, and one enantiomeric compound was isolated in the solid state: C. D. Pentecost, A. J. Peters, K. S. Chichak, G. W. V. Cave, S. J. Cantrill, J. F. Stoddart, *Angew. Chem.* **2006**, *118*, 4205–4210; *Angew. Chem. Int. Ed.* **2006**, *45*, 4099–4104.

[45] Molecular deformations in some vibrational states will impart chirality to a molecule of methane and, as a result, at any time, individual molecules will almost always be chiral. The cancellation of two exactly mirror-image structures may only be asserted on a statistical basis; see Ref. [16] and especially the discussion on pp. 22–26.

[46] M. Hampe, *Angew. Chem.* **2006**, *118*, 1044–1048; *Angew. Chem. Int. Ed.* **2006**, *45*, 1028–1031.

[47] U. Grenander, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 783–789.

[48] a) L. D. Barron in *New Developments in Molecular Chirality* (Ed.: P. G. Mezey), Kluwer, Dordrecht, **1991**, pp. 1–55; b) L. D. Barron, *Chirality in Natural and Applied Science* (Eds.: W. J. Lough, I. W. Wainer), Blackwell, Oxford, **2002**, pp. 53–86; c) L. D. Barron, *Molecular Light Scattering and Optical Activity*, 2nd ed., Cambridge University Press, Cambridge, **2004**, pp. 38–52.

[49] a) G. Priest, *Contradiction*, Clarendon Press, Oxford, **1987**; b) G. Priest, *Doubt Truth to Be a Liar*, Clarendon Press, Oxford, **2006**.

[50] J. Polanyi, *Queen's Quart.* **2000**, *107*, 31–36. I thank Roald Hoffmann for providing this quotation in his lecture "Honesty to the Singular Object", which he gave, for example, in Lindau, Germany, in June 2006.

[51] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 5.

[52] In a broad sense asymmetric (or asymmetrical) means lacking symmetry, misproportionated, or simply unequal. The latter is the common use of asymmetry in biological sciences: not equal in quantity, size, rank, value, etc. (see Section 6 of this essay). In physics, the terms asymmetric, antisymmetric, and nonsymmetric as applied to wave functions follow the sense attributed in logic, that is, a relation never holding between a pair of values *x* and *y* when it holds between *y* and *x*.

[53] Most examples of stereodifferentiating reactions can likewise be labeled "mirror-image symmetry breaking" (not chiral symmetry breaking) processes. See:

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a) D. M. Walba, *Top. Stereochem.* **2003**, *24*, 457 – 518; b) M. Ávalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron: Asymmetry* **2004**, *15*, 3171 – 3175.

[54] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, Chap. 6, especially pp. 153–155.

[55] Mislow alludes to a previous exhortation by F. M. Jaeger: *Retournons à Pasteur!*; for an extended commentary, see: K. Mislow, *Top. Stereochem.* **1999**, *22*, 27.

[56] a) R. B. King, *Advances in Biochirality* (Eds.: G. Pályi, C. Zucchi, L. Caglioti), Elsevier, Amsterdam, **1999**, pp. 13 – 34; b) *Chemical Explanation: Characteristics, Development, Autonomy* (Ed.: J. E. Earley, Sr.), International Society for the Philosophy of Chemistry: Summer Symposium on the Philosophy of Chemistry and Biochemistry, **2002**; R. B. King, *Ann. NY Acad. Sci.* **2003**, *988*, 158 – 170.

[57] P. G. Mezey, *Advances in Biochirality* (Eds.: G. Pályi, C. Zucchi, L. Caglioti), Elsevier, Amsterdam, **1999**, pp. 35 – 46, and references therein.

[58] Alfred Werner attempted the resolution of the enantiomeric complexes of *cis*-[Co(en)$_2$(NO$_2$)$_2$]Cl (en = ethylenediamine) which took considerable effort. In 1901, Werner's first female doctorate student, Edith Humphrey, obtained optically active crystals by spontaneous resolution but it was not recognized. Werner's oversight was not recognized until 86 years later: a) I. Bernal, G. B. Kauffman, *J. Chem. Educ.* **1987**, *64*, 604 – 610; I. Bernal, *Chem. Intell.* **1999**, *5*, 28 – 31.

[59] F. Wilczek, *Nature* **2005**, *435*, 152 – 153.

[60] Symmetry breaking and symmetry violation can be distinguished as two different concepts. For an excellent discussion see L. D. Barron, *Molecular Light Scattering and Optical Activity*, 2nd ed., Cambridge University Press, Cambridge, **2004**, pp. 213 – 216. Barron also points out the influence of parity violation on the natural optical activity. The tiny natural optical rotation shown by a free atomic vapor is due solely to parity violation, which is constant in time.

[61] In physics the term chiral symmetry is equivalent to congruence of two mirror-image objects, that is, it refers to an achiral species in chemical terms.

[62] For instance: B. Schwarzschild, *Phys. Today* **2005**, *58* (Sept. issue), 23 – 25.

[63] a) M. Levin, *Mech. Dev.* **2005**, *122*, 3 – 25; b) A. Raya, J. C. Izpisúa Belmonte, *Nat. Rev. Genet.* **2006**, *7*, 283 – 293; c) S. Hozumi, R. Maeda, K. Taniguchi, M. Kanai, S. Shirakabe, T. Sasamura, P. Spéder, S. Noselli, T. Aigaki, R. Murakami, K. Matsuno, *Nature* **2006**, *440*, 798 – 802; d) P. Spéder, G. Adám, S. Noselli, *Nature* **2006**, *440*, 803 – 807.

[64] a) J. Dzik, *Evol. Biol.* **1993**, *27*, 339 – 386; b) A. R. Palmer, *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14279 – 14286; c) M. Levin, *Advances in Biochirality* (Eds.: G. Pályi, C. Zucchi, L. Caglioti), Elsevier, Amsterdam, **1999**, pp. 137 – 152.

[65] A specialized journal is currently available, *Laterality: Asymmetry of Body, Brain, and Cognition*.

[66] C. McManus, *Right Hand, Left Hand: The Origins of Asymmetry in Brains, Bodies, Atoms and Cultures*, Harvard University Press, Cambridge, MA, **2002**, pp. 1 – 6.

[67] Cover page of the issue containing: D. Ajami, K. Hess, F. Köhler, C. Näther, O. Oeckler, A. Simon, C. Yamamoto, Y. Okamoto, R. Herges, *Chem. Eur. J.* **2006**, *12*, 5434 – 5445.

[68] H. Brunner, *Rechts oder links—in der Natur und anderswo*, Wiley-VCH, Weinheim, **1999**.

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