HISTORY

Molecular Chirality in Chemistry and Biology: Historical Milestones[1])

by **Joseph Gal**[2])

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Beginning early in the 19th century, developments in crystallography, optics, and chemistry in France set the stage for the discovery of molecular chirality by *Louis Pasteur* in 1848. He found that the crystallization of the sodium ammonium salt of '*paratartaric acid*', a mysterious '*isomer*' of natural (+)-tartaric acid (TA), produced two different crystal types that were non-superimposable mirror-image forms of each other. He separated the two types and found their optical rotations in solution opposite in direction and equal in absolute magnitude. This led him to conclude that paratartaric acid is a combination of two mirror-image molecule types of TA that are '*dissymmetric*', an existing term he adapted to the connotation of today's '*chiral*'. In 1857, he found that the two enantiomers of TA were metabolized by a microorganism at drastically different rates, and thereby discovered biological enantioselectivity. In 1886, Italian chemist *Arnaldo Piutti* discovered D-asparagine and found that it tasted intensely sweet, in contrast to the known L-asparagine which had no taste. This was the discovery of stereoselectivity at biological receptors. As a result of advances in stereoselective synthesis and enantioselective chromatography during the last decades of the 20th century, in the 1990s the importance of molecular chirality in drug action and disposition began to receive serious attention from drug-regulatory authorities and the pharmaceutical industry, the overall result of which has been the near-complete disappearance of racemic drugs as newly introduced pharmaceuticals.

1. Introduction. – In this article, some historical aspects of molecular chirality are chronicled. The focus here is on chirality because this facet is considered by many the richest and most captivating component of stereochemistry. *Mirror-image incongruence*, *i.e.*, the non-superimposability of certain objects on their mirror image (that is, *handedness*), is indeed a fascinating phenomenon, with a variety of manifestations in

[1]) From January to August 2013, *Helvetica Chimica Acta* have featured eight consecutive Reviews under the general title '*Organic Stereochemistry*'. Together with additional material, these articles are now being prepared as individual chapters for publication in a book titled '*Organic Stereochemistry – Guiding Principles and Biomedicinal Relevance*' and edited by *Bernard Testa*, *M. Volkan Kisakürek*, and *John Caldwell*. Among the additional material alluded to, a concluding chapter was planned which would offer an overview of historical milestones of particular stereochemical significance. The Editors gratefully acknowledge the enthusiastic response of Prof. *Joseph Gal*, perhaps *the* world expert in the field. As with the eight chapters, pre-publication seemed desirable and is offered herewith to the readership of *Helvetica Chimica Acta*.

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many aspects of our world [1]. But why should we be interested in the historical aspects of science? One incisive answer to this question was given by Sir *Hans A. Krebs* (1900–1981, *Nobel* Laureate in Physiology or Medicine, 1953): '*Those ignorant of the historical development of science are not likely ever to understand fully the nature of science and scientific research.*' [2].

The first known serious examination of the property of handedness was carried out by the German philosopher *Immanuel Kant* (1724–1804) during the second half of the 18th century, in the context of a debate among philosophers on the nature of space [3][4]. Referring to the two hands, *Kant* wrote that '*sie können nicht kongruieren*' ('*they are not congruent*' [3] (translations are by the present author), and called such objects *incongruent counterparts* [4]. In chemistry, the science of molecular chirality is a large domain [5], with crucial implications in biology [6]. Moreover, the development of this science has had a long history (see below), and, therefore, in a forum such as this article, it would be unrealistic to attempt to provide a comprehensive account. Thus, inevitably, the present review can cover only a selection from that history and, naturally, the material chosen for inclusion here reflects to some extent the bias of the author. However, it is hoped that the historical events described, all milestones within the development of the science, will provide a useful and thought-provoking backdrop to organic stereochemistry.

2. The Discovery of Molecular Chirality. – *Louis Pasteur* (1822–1895; *Fig. 1*) has been widely admired around the world for well over a century for his seminal discoveries in microbiology and infectious diseases which were of immense benefit to human health, veterinary medicine, agriculture, *etc.* [7]. Less-well known (especially outside the chemistry community) is the fact that he began his career as a chemist and, at the age of 25, just after earning his doctorate, made one of the most important discoveries in chemistry, namely, that of molecular chirality.

Pasteur was born into a modest family in Dole, in the *département* (administrative district) of Jura in the Franche-Comté region of eastern France [7]. His father, *Jean Joseph Pasteur*, was a tanner; his mother, *Jeanne Étiennette* (*née Roqui*) was a homemaker. *Pasteur* obtained his first university degree in 1845 (*i.e.*, he became *licencié ès sciences*) at the *École normale supérieure* (ENS) in Paris. In 1846, he earned his *agrégation* (French state licensure to teach in secondary schools or higher-education institutions), and in October, 1846, became *agrégé-préparateur* (a sort of teaching or laboratory assistant) for chemistry professor *Antoine-Jérôme Balard* (1802–1876) at the ENS [7]. *Pasteur* also undertook research projects in *Balard*'s laboratory at that time. Before we describe *Pasteur*'s discovery, however, we need to digress briefly to put *Pasteur*'s choice of research projects and eventually his discovery of molecular chirality in the context of the relevant French scientific traditions of the first half of the 19th century. This history has been exquisitely analyzed by *Mauskopf* [8] and will be addressed here only briefly.

2.1. *Background to* Pasteur*'s Discovery.* It is important to recognize that *Pasteur*'s discovery was rooted in, and benefited from, the great 19th-century French traditions in the fields of crystallography, optics, and chemical structuralism (*i.e.*, theories of the arrangement of atoms in organic molecules) [8]. In all of these areas, French scientists made major contributions during the *ca.* 50–60 years preceding *Pasteur*'s discovery of

Fig. 1. Louis Pasteur*'s official portrait as a member of the Académie française* (courtesy of the Académie française)

molecular chirality in 1848. In crystallography, some of the prominent names to be mentioned include *René Just Haüy* (1743 – 1822), *Gabriel Delafosse* (1796 – 1878), and *Auguste Laurent* (1808 – 1853); in optics, *Étienne Louis Malus* (1775 – 1812), *François Jean Arago* (1786 – 1853), and *Jean-Baptiste Biot* (1774 – 1862); in theories of chemical structure, *André-Marie Ampère* (1775 – 1836), *Marc Antoine Gaudin* (1804 – 1880), *Alexandre Édouard Baudrimont* (1806 – 1880), *Jean-Baptiste Dumas* (1800 – 1884), and *Auguste Laurent* were leading figures. There were other important scientists in all of these domains (some outside France), and the reader is referred to *Mauskopf*'s article [8] for the details. Of immediate relevance to *Pasteur*'s work were *Biot*, *Delafosse*, and *Laurent*.

In 1808, *Malus* discovered polarized light [9], and in 1811 *Arago* discovered optical rotation (by slices of quartz crystals) [10]. It was *Biot* (*Fig. 2*), however, who, beginning in 1812, carried out, over a period of several decades, a great deal of important and pioneering work in the field of optical activity [12]. In 1817, he announced his finding [13] that a number of natural compounds, including sucrose, oil of turpentine, camphor, and tartaric acid (TA), rotated polarized light in the non-crystalline state, *i.e.*, in solution, or in the liquid or vapor phase, work that was to be of great importance for *Pasteur*'s subsequent studies [14]. Upon *Pasteur*'s discovery of molecular chirality, *Biot* became his ardent supporter and mentor [15], and *Pasteur* revered *Biot* [16].

In crystallography, *Delafosse*, a student of *Haüy*, continued and refined his mentor's pioneering work in crystallography and theories of crystal structure, and was also *Pasteur*'s professor of mineralogy at the ENS. *Delafosse* strongly emphasized in his lectures the importance of *hemihedrism* in crystallography, and *Pasteur* later did not fail to remember his professor's advice when he came to examine the crystals of TA and

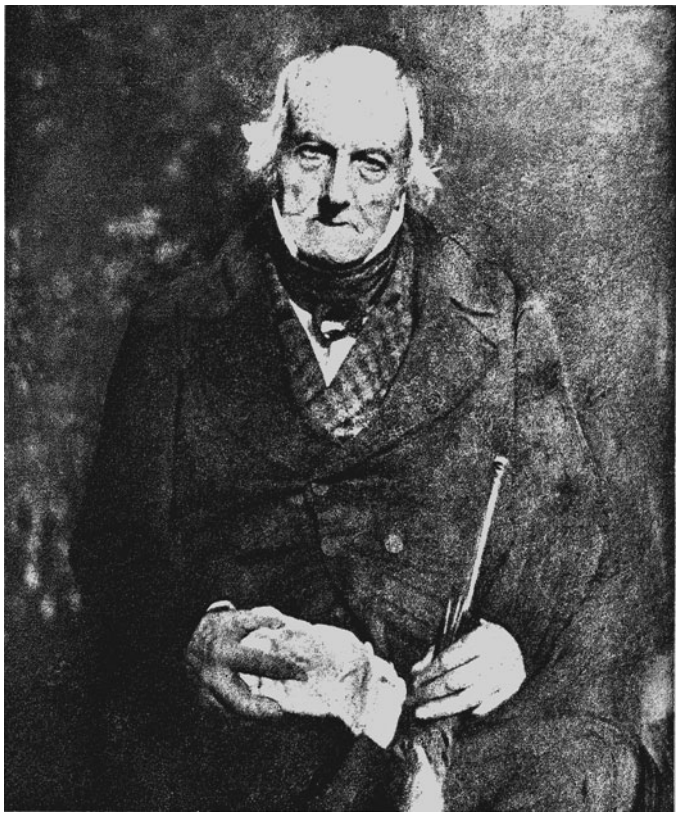

Fig. 2. Jean-Baptiste Biot (reprinted from [11])

related compounds [17] (*holohedral* crystals have the highest symmetry within a given crystal system, while in *hemihedral* crystals certain additional facets appear at edges or corners of the basic crystal form but only in one-half the number required by *Haüy*'s law of symmetry, and such hemihedrism degrades the symmetry of the crystals).

Laurent deserves special mention. (Most sources, *e.g.* [18], give 1807 as the year of his birth, but some, *e.g.* [19], including the respected historian of chemistry *J. R. Partington* [19a] and *L. Pasteur Vallery-Radot* (*LPVR*), *Pasteur*'s grandson [19d], indicate it as 1808.) *Laurent* was a brilliant chemist who produced an extraordinarily large amount of varied and highly original work, *e.g.*, in organic synthesis, structural studies, crystallography, systematization of organic chemistry, theories of structure and reactions, chemical nomenclature, *etc.* [20–22]. He was an excellent experimentalist; his theories of organic chemical structure and reactions were revolutionary and important for the subsequent development of structural organic chemistry by *Kekulé*, *Butlerov*, and others [20–22]. His professional career was, however, unsuccessful; he was rejected by the French scientific elite, and he died of tuberculosis in 1853, at age 44 [22].

For a few months beginning in late 1846 [19d][23] and lasting until April 1847 [24], *Laurent* worked in *Balard*'s laboratory at the ENS. *Pasteur* made *Laurent*'s acquaintance there [25] and undertook research projects suggested and guided by *Laurent* [14][23]. In August, 1847, *Pasteur* earned his doctorate (*docteur ès sciences*) at the Faculté des Sciences in Paris with two dissertations, one in chemistry [26] and another in physics [27], based on work he carried out in *Balard*'s laboratory. It is noteworthy that a great deal of *Pasteur*'s doctoral work was based on research ideas suggested by *Laurent* [14][20][26][27], and *Pasteur* gratefully acknowledged his debt to *Laurent* [26][27].

2.2. Pasteur *Discovers Molecular Chirality.* Sometime in late 1847 or early 1848, *Pasteur* began new investigations of the crystallography of '*natural*' TA and some of its salts [28]. TA was obtained from the fermenting grape juice in the wine-making process, and it was known that the substance was optically active and dextrorotatory, but its chemical structure was unknown at the time (the three stereoisomeric TAs are shown in *Fig. 3*). In the course of these studies, *Pasteur* also investigated a mysterious '*isomer*' of (+)-TA known as '*racemic acid*' or '*paratartaric acid*' (PTA) which had been isolated on a single occasion, *ca.* 1819, in a factory producing natural (+)-TA from fermenting grape juice in Alsace, France [29] ('racemic' derives from '*racemus*', Latin for a cluster of grapes). PTA was known to be optically inactive [29]. Today, (+)-TA is known to have the (2*R*,3*R*) configuration (*Fig. 3*).

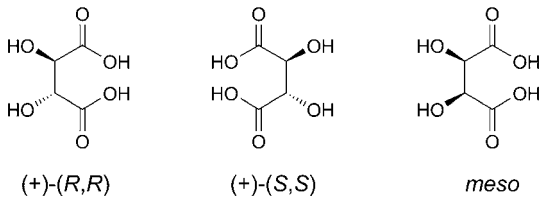

Fig. 3. *The stereoisomers of tartaric acid (TA)*

Although by the time *Pasteur* began his TA studies *Laurent* was no longer at the ENS, it is clear that *Pasteur*'s design of the tartrate studies was also significantly influenced by *Laurent*'s ideas [14][20]. Indeed, the precepts and goals of these studies were rooted in *Laurent*'s theories and investigations aimed at obtaining information on the arrangement of atoms in molecules from studies of the details of crystal structure. The methodology for these considerations included studies of the basic crystal systems of the substances: examination of crystal isomorphism (*i.e.*, the phenomenon of different compounds having the same or very similar crystal structures), dimorphism (the occurrence of two different crystal structures of a single compound), hemihedrism; determination of the number of waters of hydration, analysis of the precise elemental composition of the compounds, *etc.*

In these investigations, *Pasteur* examined (natural) (+)-TA and a dozen of its salts, and PTA and several of its salts. He painstakingly studied and compared the crystals of the various compounds, hoping to systematically determine similarities and differences

among the crystals and relate such information to the chemical composition and molecular nature of the substances [14].

In the course of these studies, in April, 1848, *Pasteur* came to compare the crystal structure of sodium ammonium tartrate to that of the corresponding sodium ammonium salt of PTA. He was aware of a report [30] from 1844 in which the German chemist and crystallographer *Eilhard Mitscherlich* (1794–1863) claimed that these two salts had identical, completely indistinguishable, crystal forms, despite the fact that the tartrate compound was optically active, while the paratartrate had no optical activity. It appears that when *Pasteur* examined the two salts he may have recalled *Mitscherlich*'s report and wondered about the supposed complete identity of the crystal forms despite the difference between the two substances in optical activity [14].

Armed with his training in crystallography by *Delafosse* and *Laurent* (both of whom had taught him to pay close attention to the fine details of crystal morphology), *Pasteur* first found that the crystals of the tartrate salt were hemihedral, and the direction of the hemihedrism was constant. That is, when he oriented and viewed the crystals in a consistent manner according to an arbitrary convention, two of the hemihedral facets occurred only on the left side of the tartrate crystals. When he examined the paratartrate crystals, however, he found, to his surprise, that the salt crystallized as a mixture (a conglomerate, in today's terminology) of two types of crystals. On close examination, he found that one of the crystal types appeared identical to the crystals of the sodium ammonium salt of natural (+)-TA, while in the other, mirror-image, crystals the hemihedrism was in the opposite direction to that of the tartrates [31]. Importantly, he found that the two crystal forms were non-superimposable-mirror-image versions of each other (*i.e.*, enantiomorphous, by todays terminology). *Pasteur*'s own drawing of the two crystals are shown in *Fig. 4*.

Pasteur manually separated the two enantiomorphous crystal types of the PTA salt and dissolved the two forms separately to measure their optical activity [32]. He found the rotations to be equal (within experimental error) in absolute magnitude but opposite in direction (actually, initially, the optical rotation values differed somewhat due to difficulties *Pasteur* encountered in his attempts to cleanly separate the two crystal types, difficulties that were caused by the fusion – called 'twinning' today – of some of the enantiomorphous crystals [32]; soon, however, he managed to obtain pure crystals that produced optical rotations equal in absolute magnitude [33]). The free TAs *Pasteur* obtained from the salts had enantiomorphous crystal morphology and optical rotations equal in absolute value and opposite in direction.

This was the discovery of the first example of a racemic mixture (PTA) and the first example of a substance both of whose enantiomers were identified. Moreover, most importantly, *Pasteur*'s findings led him to the realization that the molecules of TA had to be *chiral*, *i.e.*, he discovered *molecular chirality* [34]. The 25-year-old *Pasteur* read his memoir on the discovery to the *Académie des sciences* (Academy of Sciences, Académie henceforth) in Paris on May 22, 1848 [31][35].

As discussed above, *Pasteur*'s discovery was made possible by the work during the preceding *ca.* 50 years in crystallography, optics, and chemistry by scientists primarily in France [8][14]. As also mentioned above, the immediate influences of *Biot*, *Delafosse*, and *Laurent* on *Pasteur* were important. *Pasteur* recognized the debt of authors of

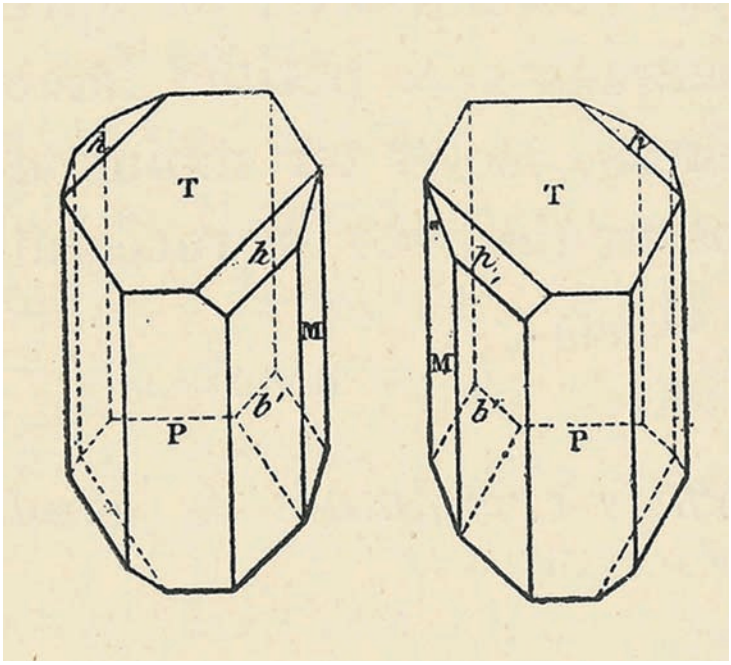

Fig. 4. Pasteur*'s drawing of the enantiomorphous crystals of sodium ammonium tartrate* (reprinted from [31])

scientific discoveries to those who preceded them; in 1858 he wrote: '[*une découverte*] *n'est jamais l'œuvre d'un seul homme*' ('*a discovery is never the work of one man alone*') [36]. It has been pointed out, however, that, after his discovery of molecular chirality, *Pasteur* gave no credit to *Laurent* for his guidance and influence [37]. One historian attributed this lapse to a lack of ethics and crude career opportunism on the part of *Pasteur* [37a], but others have been less harsh on *Pasteur* in this regard [37b][38]. It is indeed clear, as discussed above, that the precepts of *Pasteur*'s TA studies had their basis in *Laurent*'s ideas and work [14][20], but in weighing *Pasteur*'s conduct in this matter of the credit due to *Laurent*, it is also essential to recognize that, in the final analysis, *Pasteur*'s discovery of molecular chirality was neither predicted nor explained by *Laurent*'s theories [20][39]. Moreover, *Pasteur*'s originality in the discovery is also demonstrated by the fact that several of his eminent crystallographer predecessors, *e.g.*, *de La Provostaye*, *Mitscherlich*, and *Hankel* who also studied the crystallography of the tartrates [8], failed to discover molecular chirality.

For the next *ca.* ten years, *Pasteur* carried out a great deal of additional work [40] on crystal and molecular chirality, and his findings were of considerable importance. For example, he discovered the thermal interconversion (racemization) of the TA enantiomers; he discovered *meso*-TA (*Fig. 3*) and understood that the reason for its optical inactivity was its inherent non-chiral molecular structure; he recognized chiral diastereoisomerism; he discovered the resolution of racemates *via* fractional crystallization of diastereoisomeric salts; he discovered biological enantioselectivity when he

examined the microbial metabolism of racemic TA [41][42]; he discovered and studied the molecular and crystal chirality of many natural compounds, *etc.* [40]. Overall, his work on molecular chirality is considered the foundation of stereochemistry.

3. From the History of the Language of Chirality: *Dissymmetry*. – Why study the language of science? As discussed elsewhere, there are several compelling reasons for such studies [43]. In the present context, investigations of the language of a scientific discipline can be revealing about the development of the science itself, since the evolution and change of the language is a reflection of the historical development of the science. Stereochemistry is a rich and complex discipline [5], and, therefore, its language is also rich and complex. However, few studies have been published on the history of this language.

When he discovered molecular chirality, *Pasteur* recognized that a term was needed for the designation of the phenomenon of handedness in chemistry and crystallography, and adopted *dissymétrie* (dissymmetry) and its adjective form *dissymétrique* (dissymmetric) for the purpose [43a]. A few authors [5a][44] have briefly commented on *Pasteur*'s *dissymétrie*, but considerable confusion exists in the literature concerning the term's history, meaning, and its use by *Pasteur* and others [43a]. It seems of interest, therefore, to consider in detail this fundamental term in the history of stereochemistry.

3.1. *Stereochemical Terminology in the 19th Century.* In the middle of the 19th century, at the time of *Pasteur*'s discovery, organic chemistry was in its early infancy [45]. Elemental analysis was already on solid grounds, but little else was understood about organic molecules or reactions. Thus, there was no comprehension of valence, chemical affinity, chemical structure, or stereochemistry. However, by 1830 several sets of compounds had been discovered where the (two) members of each set had the same elemental composition but different properties. Among these sets were silver cyanate and silver fulminate, ammonium cyanate and urea, and TA and PTA. However, no understanding of the structural basis of this phenomenon was possible at the time. To provide terminology for the phenomenon, the Swedish chemist *Jöns Jakob Berzelius* (1779–1848) coined the terms *isomer* and *isomerism* [46].

Structural organic chemistry progressed during the century, and in 1861 '*chemical structure*' was coined by the Russian chemist *Aleksandr Butlerov* (1828–1886), but this term was used to refer to *chemical constitution* rather than to the three-dimensional, geometric, arrangement of the atoms in the molecule [47]. In 1874, *Jacobus Henricus van't Hoff* (1852–1911) discovered what he called the *asymmetric carbon atom* [48]. With the further progress in the understanding of organic structure came, during the last two decades of the 19th century, the introduction of several additional terms relevant to stereochemistry. Thus, in 1886 the German chemist *Aemilius Wunderlich* (about whom very little is known) introduced *configuration* [49], and in 1889 another German chemist, *Viktor Meyer* (1848–1897), coined *stereochemistry* [50]. *Chirality* and *chiral* were introduced in 1894 by the British physicist Sir *William Thomson* (1824–1907; known as Lord *Kelvin*) [51].

Pasteur, however, did not use the terms introduced by *Butlerov*, *Wunderlich*, *Meyer*, or Lord *Kelvin*. By the end of the 1850s, he had abandoned experimental work on chirality and moved on to microbiology [42], and although he continued to lecture and write commentaries on molecular chirality after his change of research direction, it is

clear that he did not follow the development of structural organic chemistry and its implications for molecular chirality [52]. In his lectures and commentaries on chirality from 1860 into the 1880s, his language – and indeed his science – of molecular chirality remained 'frozen' at the state of knowledge of the 1850s.

3.2. *Etymology and Pre-*Pasteur *History of* Dissymétrie. The term *dissymétrie* was not *Pasteur*'s coinage; in fact, it appeared in the French scientific literature well before *Pasteur* arrived on the scene (indeed, even before he was born). In a lecture [53] presented in February 1820 (and published in 1821), the Swiss mineralogist (and later numismatist) *Frédéric Jacob Soret* (1795–1865) described (in French) the form of the crystals of aragonite (a form of calcium carbonate) as *dissimétrique* [*sic*] to indicate that they lacked certain symmetry properties relative to the crystal axis. In 1824, *Biot* also spelled the terms as *dissimétrie* and *dissimétrique* in referring to the *difference* seen in optical rotation by certain substances, namely, that some compounds rotate the plane of polarized light to the right while others to the left [54]. In a lecture in 1832 (published in 1835), *Biot* again used the term (this time spelled *dissymétrique*) to express the difference in optical rotation [55]. In 1835, in a volume on mineralogy (in French), the Swiss crystallographer *Louis Albert Necker* (1786–1861) used *dissymétrie* and *dissymétrique* to refer to crystals that did not obey *Haüy*'s law of symmetry, which required that identical parts of the crystal be modified in the same manner when additional faces (or facets) modify a simpler crystal habit. *Necker* stated that '*… crystals of this type, modified at the corners, are usually dissymmetric, which is to say that only one-half of their solid angles suffer such modifications*' [56]. In 1842, the French engineer and scientist *Antoine-César Becquerel* (1788–1878) also used *dissymétrie* in the context of the violation of *Haüy*'s law of symmetry [57]. Discussing hemihedral boracite crystals (which have a non-chiral morphology), he wrote: '*… one of the angles is modified and the other is not, which introduces a dissymmetry, since the two angles are identical and should be modified simultaneously*' [57]. Finally, in 1846 the French agricultural chemist *Joachim Isidore Pierre* (1812?–1881) wrote the following in an article on certain metal salts: '*Double sulfate of manganese and potassium. This compound, which is obtained by mixing, equivalent for equivalent, solutions of the two single sulfates, appears in the form of very-slightly-pink-tinted white flakes, which appear to belong to the prismatic system with rhomboid base by virtue of the dissymmetry of their modifications*' [58]. Here again, the unequal modifications of the crystal morphology are termed a '*dissymmetry*'.

Dissymmetry first appeared in a French dictionary in 1846 [59]. It was spelled *dyssymétrie*, which is the combination of a variant of the Greek prefix *dus,* which expresses the concept of a lack or absence, and *symétrie*, *i.e.*, symmetry (the prefix *dus* and its *dys* variant should not be confused with *dis*, a Latin prefix). The definition given in the dictionary was '*lack of symmetry*', and the crystallographic context mentioned above was used as an example of usage but no citations were provided [59]. Another source, the *Dictionnaire des Synonymes* (Dictionary of Synonyms) of the *Laboratoire CRISCO,* gives the following synonyms for dissymmetry: asymmetry, discordance, irregularity [60]. In addition, Dr. *Christopher Braider*, Professor, Department of French and Italian, University of Colorado, Boulder, CO, USA, has provided the following information to the present author: '*As to usage, 'asymétrique' (asymmetric)*

means 'lacking in symmetry'. By contrast, 'dissymétrique' suggests a disruption, disturbance, or destruction of symmetry.'

All in all, while the individual who coined *dissymétrie* has not been identified, it is clear that the term had been in use in scientific French for several decades before *Pasteur* embraced it. It is also evident from all of the above that the meaning of *dissymétrie* in the first half of the 19th century included a disruption or reduction of symmetry and the resulting implication of an *imbalance*, *dissimilarity*, or *difference* in structure, appearance, or function between two objects or parts of an object or two phenomena. During the period in question, the usage of the term did not include the connotation of handedness specifically, and, indeed, none of the above-cited examples of the use *dissymmetry* refer explicitly to chirality.

3.3. Pasteur*'s* Dissymétrie*: The First Appearance. Pasteur* read his first report on the spontaneous resolution of sodium ammonium tartrate to the *Académie* in Paris on May 22, 1848 [31][36–39]. An excerpt of *Pasteur*'s oral presentation was published in the proceedings of the *Académie* (the '*Comptes rendus*') under the title '*Memoir on the relationship that may exist between crystalline form and chemical composition, and on the cause of optical rotation*' [31]. The memoir has been translated into English [61], but in the present article the original in French [31] will be used as the basis for the analysis. The contents and language of the memoir deserve a detailed examination in the present context. What exactly does it contain concerning the chirality of molecules and the morphological chirality of crystals, and what is the relevant language *Pasteur* used?

A word of caution is in order here: the memoir as it appears in the *Comptes rendus* [31] constitutes only an excerpt from the text *Pasteur* read at the session of the *Académie*, as indicated by the word '*extrait*' (*i.e.*, extract, excerpt, abstract) after the title in the publication. The precise text of *Pasteur*'s lecture is in fact not known as no verbatim transcript has been published.

It needs to be emphasized here that *Pasteur*'s memoir says *nothing explicitly about mirror images or about chirality of any kind, whether in crystal habit or in molecular structure* [31][43a]. *Pasteur* begins his memoir with a discussion of the crystal habit of a series of tartrate and paratartrate salts, and points out the presence of hemihedrism in the former and its lack in most of the latter. Referring to the tartrate crystals, he explains that hemihedrism modifies the two '*extremities*' (*i.e.*, the two ends of the crystal along the crystal axis) in such a manner that '*les deux extrémités du prisme sont dissymétriques*' ('*the two extremities of the prism are dissymmetric*'). This use of the term is clearly in the sense of '*dissimilar*' or '*different in appearance*'. In the next sentence, *Pasteur* states that '*Haüy's famous law, which requires that identical parts be modified in the same manner, is violated*.' Thus, *Pasteur*'s use of '*dissymmetry*' here puts emphasis on his finding that the two extremities of the tartrate crystal are modified differently by hemihedrism, *i.e.*, the edges and angles are affected differently at one extremity than at the other (in violation of *Haüy*'s law of symmetry), but, importantly, nothing is mentioned or implied about chirality or enantiomorphism [31][43a].

Later in the memoir [31], speaking of the two types of crystals he identified in sodium ammonium paratartrate, *Pasteur* says: '*Here now is the crystallographic difference between these two types of crystals. They are all hemihedral; but some are hemihedral to the right, others to the left, and the direction of* [optical] *rotation depends on this dissymmetry*'. Again, there is a disruption or reduction in the symmetry, and the

difference in the appearance of the two types of hemihedral facets is qualified as *a dissymmetry*, while nothing is said about non-superimposable mirror images. It is relevant in this context that in none of his prior publications or two doctoral theses had *Pasteur* mentioned the word *dissymmetry*, the concept of chirality, reflection symmetry, or hemihedrism causing chirality in a crystal.

Dissymétrie appears twice in the memoir, as does *dissymétrique* [31]. All four instances are in the sense discussed above, *i.e.*, to denote a dissimilarity in the appearance of two entities, without any reference to chirality. The fourth and final appearance of the terminology in the memoir, however, merits amplification. The term occurs in the following sentence: '*Is it not evident by now that the property of certain molecules of rotating the plane of polarization has as its cause, or at least is linked in a most intimate manner to, the dissymmetry of these molecules*?' It is tempting to interpret '*dissymmetry*' in this sentence as specifically referring to the chirality of the molecules, but the evidence, taken in its entirety and in context, indicates unequivocally that such a conclusion would be unjustified. As discussed above, the subject of mirror images or chirality is entirely absent from the memoir, and it is clear from the text following the sentence that, in referring to the '*dissymmetry*' of the molecules, *Pasteur* is making an extrapolation from one correlation (between the direction of the leaning of the hemihedral facets and the direction of optical rotation) to a similar correlation, *i.e.*, between the direction of optical rotation by TA and a presumed dissimilarity, *i.e.*, a dissymmetry, in the structure of the two types of TA molecules. At this point, the nature of the dissymmetry has not been specified.

Therefore, it is clear that '*dissymmetry*' in the sentence in question expresses a certain presumed difference in the structure of the two molecules, without, however, any indication of the nature of this phenomenon and specifically without any allusion to chirality. Whether in the actual lecture *Pasteur* did in fact refer to handedness cannot be determined without the verbatim record of the lecture. However, as will be seen shortly, *Pasteur* soon introduces a clarification, an explanation, of the type of dissymmetry he has in mind (see below) [31][43a].

3.4. *The Full Article in* Annales de Chimie et de Physique. *Pasteur*'s memoir in the *Comptes rendus* discussed above was short and did not contain experimental details (brevity was in fact a requirement of publishing in the *Comptes rendus* [62]). It is also clear that in the published memoir he employed the terms *dissymétrie* and *dissymétrique* without introducing the concept of chirality. Nevertheless, it appears that by the time he read the memoir at the *Académie*, he was most likely aware of the non-superimposable-mirror-image morphology of the crystals and had formulated in his mind the proposal that the molecules of TA must be chiral. This is suggested by the contents of his subsequently published expanded and detailed article on the same work in the *Annales de Chimie et de Physique* (*Annales* henceforth) which appeared in the same year, 1848 [34].

The *Annales* article [34] is 16 pages long and is divided into two parts. In the first part, *Pasteur* describes the crystallographic properties of natural (dextrorotatory) TA, and a series of tartrate and paratartrate salts. He reports finding evidence for hemihedry in most of the tartrates and TA and for its absence in the paratartrates. He describes the hemihedral crystals as *dissymmetric* in the sense that the two extremities

of the crystals are modified unequally, differently, and in violation of the law of symmetry.

In the second part of the article, *Pasteur* examines the sodium ammonium salt of (+)-TA and the corresponding salt of PTA. He finds two crystal types in the paratartrate salt and describes them as '*isomorphous … but the isomorphism here is unprecedented: it is the isomorphism of two dissymmetric crystals facing one another in a mirror*'. *Pasteur*'s language here comes close to, but does not actually equal, the definition of *dissymmetric* as synonymous with '*handedness*' [35][43a].

But then *Pasteur* finally does provide that definition when he describes the two crystal types as '*dissymmetric, and the dissymmetry of one of them is the dissymmetry of the other seen in a mirror*' [35]. This then is his first clear indication that he is now using '*dissymmetry*' to refer to that character of the crystals in question which renders them not-superimposable on their mirror image [43a].

At this stage, *Pasteur* does not, however, apply '*dissymmetry*' directly to the molecules of TA; instead he describes the enantiomeric molecules as '… *two atomic groups that are symmetrically isomorphous*'. He also applies similar terminology to the enantiomorphous crystals: '… *these two species of crystals, which do not differ in any manner except in the symmetry of the position of the image in the mirror relative to the original*'. Moreover, in the article he also describes enantiomorphous objects as '*symmetric but not superposable*' [35]. According to *Delafosse*, the use of '*symmetric*' to describe the relationship of two objects that are non-superimposable mirror images of each other was introduced by the French mathematician *Adrien-Marie Legendre* (1752 – 1833), but *Delafosse* strongly objected to the use of *symmetric* in this sense [63]. In this usage, *symmetric* expresses the notion that the two objects are *isometric* (not to be confused with *isomeric*) but related as object and its non-superposable mirror-image, *i.e.*, are *enantiomorphous,* by today's terminology.

3.5. Dissymétrie *in Subsequent Use by* Pasteur. *Pasteur* continued to use *dissymétrie* in his writings and lectures after his initial explanation that in his usage the term referred to morphology of the non-superimposable-mirror-image kind [43a]. For some time, he continued to attach an explanation to the term that it referred to mirror-image '*dissymétrie*', but eventually there was no longer a need for the explanation and he began using it on its own with the implication that it referred to handedness. In this usage, the term of course no longer designated a comparison of two objects or molecules for dissimilarity; rather, it came to describe a spatial character (*i.e.*, the property of chirality) of a single molecule or object. For example, in 1856 he wrote: '… *the new products I just described will no doubt be seen by chemists and physicists as molecules individually dissymmetric (indicated by the optical activity of their solutions)*' [64]. By 1860, *Pasteur* was able to entitle his famous two lectures '*Recherches sur la dissymétrie moléculaire des produits organiques naturels*' ('*Investigations on the molecular dissymmetry of organic natural products*') [65], without having to spell out the 'handedness' aspect. Indeed, '*dissymétrie moléculaire*' ('*molecular dissymmetry*') became identified with *Pasteur*'s work on molecular handedness. Thus, in *Pasteur*'s usage *dissymmetry* became synonymous with Lord *Kelvin*'s future term *chirality,* both in the molecular and the crystal-morphology contexts [43a].

3.6. *Dissymmetry* vs. *Asymmetry.* Why did *Pasteur* choose the term *dissymétrie* over *asymétrie* (asymmetry) for the designation of molecular chirality? After all, *asymétrie*

was available and had been in use in French at least since 1691 [66]. In stereochemistry (and in scientific considerations of symmetry in general), asymmetry is defined [67] as the absence of all symmetry elements (other than the identity operation, *E* or *I*), *i.e.*, belonging to the (trivial) point group C_1. An asymmetric object is necessarily chiral, but a molecule (or object) may be chiral without being asymmetric, since the presence of a *simple axis* of symmetry does not preclude chirality. Thus, *asymmetry* and *chirality* are not synonymous. *Pasteur*'s choice of *dissymétrie* over *asymétrie* has been interpreted by some [44c][68] as an indication that he understood this difference between the two terms and, therefore, avoided using *asymétrie. Pasteur* himself, however, discussed neither the reasons for his preference of *dissymétrie* over *asymétrie,* nor the difference between dissymmetry and asymmetry in his published writings and lectures. It is worth mentioning that the molecules of (+)- and (−)-TA (*Fig. 3*) are in fact chiral but not asymmetric, since they have a C_2 axis of symmetry.

As discussed previously [43a], *Pasteur*'s *dissymmetry* has been frequently mistranslated as 'asymmetry', and the phenomenon of chirality is often referred to, incorrectly, as 'asymmetry'. Other problems concerning the meaning of *dissymmetry* (relative to asymmetry) also exist in the literature. For example, *dissymmetric* has been redefined by some as *chiral but not asymmetric* [69]. This is obviously different from the generally accepted definition of the term in the stereochemical context, which is that *dissymmetric* is synonymous with Lord *Kelvin*'s *chiral*, *i.e.*, non-superimposable on the mirror image, period (regardless of the presence or absence of asymmetry). This matter has been discussed in detail in [70].

3.7. *The Rest of the Story. Pasteur*'s *dissymmetry* was eventually replaced by Lord *Kelvin*'s *chirality* in general use in stereochemistry [43a]. Today *dissymmetry* is used only rarely as a synonym of chirality in the stereochemical, molecular, context [71], but the term continues to be widely employed in other chemistry contexts or other disciplines to express connotations other than chirality, *e.g.*, the absence of symmetry, reduction of symmetry, or even divergence or dissimilarity [70][72].

In conclusion, the introduction of *dissymmetry* terminology by *Pasteur* was an important element in the discovery of molecular chirality. The availability of this specific and convenient language for the phenomenon undoubtedly facilitated communication concerning the new science.

Finally, it is interesting to note that the other essential and widely used terminology in chirality, that based on *enantio* (*e.g.*, enantiomer, enantiomorph, enantioselective, *etc.*, *etc.*), was introduced in 1856 by the German crystallographer and mineralogist *Carl Friedrich Naumann* (1797–1873) [73], but *Pasteur* did not use this terminology [73b], even though he was personally acquainted with *Naumann* [74].

4. The Discovery of Biological Enantioselectivity. – In 1854, *Pasteur*, who was then professor of chemistry at Strasbourg, accepted an appointment as professor of chemistry and dean of the newly opened Faculty of Sciences at the University of Lille, in northern France [75]. This was an industrial region where agricultural and food industries had considerable economic significance, and fermentation-based manufacturing, such as the production of ethanol from sugar beets and the production of beer, were of particular importance [76].

4.1. Pasteur *Changes Research Direction.* While at Lille, in 1856, *Pasteur* abruptly changed research direction: he abandoned his nearly ten-year-long research on crystal and molecular chirality and began investigations in fermentations [42][77]. Eventually, from fermentations he moved on to infectious diseases, in what was to become his stellar career in this field.

Contradictory explanations [42][78] have been advanced for *Pasteur*'s sudden and drastic abandonment of dissymmetry in favor of microbiology, and the matter has been controversial. An analysis by the present author strongly suggests, however, that the importance of industrial fermentations in the Lille region was the principal factor in *Pasteur*'s change of research direction [42]. According to this interpretation, in November, 1856, after becoming aware of a problem in several factories in the region in their fermentative production of alcohol from beetroots, *Pasteur* undertook to study the problem [42][79]. This, then, was the beginning of his new career in fermentations. The results of his first investigation in this domain which dealt with lactic acid fermentation were published in 1857 [77].

4.2. Pasteur *Discovers the Enantioselective 'Fermentation' of PTA.* After three years in Lille, *Pasteur* moved again, this time to Paris: on October 22, 1857, he was appointed Administrator of the ENS and Director of Scientific Studies there. On December 21, 1857, shortly after his arrival in Paris, he presented a communication to the *Académie* entitled '*Memoir on Alcoholic Fermentation*' [41b]. As its title indicates, the memoir dealt with certain aspects of alcoholic fermentation, but near the end of the communication *Pasteur* said the following:

'*Before concluding, I ask for the permission of the Academy to present results to which I attach great importance. I have discovered a means of fermenting tartaric acid which readily affects ordinary right tartaric acid but involves left tartaric acid very poorly or not at all. Now, a remarkable thing, predictable from the preceding fact, is that when paratartaric acid, formed by the combination, molecule for molecule, of the two tartaric acids, right and left, is subjected to the same method of fermentation, it is resolved into the right acid which is fermented and left acid which remains intact, in such a way that the best means of obtaining left tartaric acid I know of today is to resolve paratartaric acid by fermentation*' [41b]. The description of the fermentation of '*paratartaric acid*' in the memoir [41b] of December, 1857, constitutes the first published observation of enantioselectivity in a biological process. Moreover, in modern terms, *Pasteur*'s finding was the first observation of substrate enantioselectivity in a biotransformation, *i.e.*, the differential metabolism of two enantiomerically related substances [80]. About three months after that brief announcement of the enantioselective microbial metabolism of TA, *Pasteur* presented to the *Académie* a communication devoted entirely to the subject [41a].

4.3. *'Memoir on the Fermentation of Tartaric Acid'. Pasteur* presented the new communication to the *Académie* on March 29, 1858, and it was published in the *Comptes rendus* for that session [41a]. The memoir was, as usual for articles in the *Comptes rendus*, short and contained few experimental details, concentrating mainly on the essence and interpretation of the work. *Pasteur* sometimes followed up a presentation to the *Académie* with a full paper in another journal, as he did, for example, for his announcement to the *Académie* of his discovery of molecular chirality in 1848, which was followed up with a full paper in the *Annales de Chimie et de*

Physique. He did not, however, publish a full paper on the fermentation of the TAs after his memoir of March, 1858, to the *Académie.*

An English translation [42] of the 1858 memoir [41a] is available. For (±)-TA, in the memoir *Pasteur* abandoned the name 'paratartaric acid' which he had used in the earlier communication [41b] and employed instead the other common name for the compound at the time, '*racemic acid*' (see above).

The memoir [41a] is divided into two parts. Part one dealt with the fermentation of (+)-TA, and *Pasteur* pointed out that the spontaneous fermentation of this acid had been known for a long time as a result of manufacturing accidents. He also gave some of the experimental details of the fermentation as conducted in his laboratory. The fermentation mixture contained ammonium (+)-tartrate, nitrogenous '*albuminoid*' material from plant or animal sources, and material from a previous active fermentation of TA.

In part two, the analogous incubation of (±)-TA is described. The fermentation was carried out in the same manner as that of the dextrorotatory acid, and the key experimental tool was the monitoring of the optical rotation of the mixture as the fermentation proceeded. It was found that the reaction mixture, which showed no optical rotation at first, became levorotatory as the fermentation progressed over several days. The rotation continued to increase and eventually reached a maximum, at which point the fermentation stopped. The dextrorotatory acid was no longer present in the mixture, having been destroyed in the fermentation. (−)-TA, which was not affected by the microorganism ('ferment'), could then be readily isolated in pure form from the mixture. In the remainder of the memoir [41a], *Pasteur* proposed an explanation for the selective destruction of (+)-TA in the fermentation (see below).

4.4. *Analysis of the Discovery.* As we have seen, when *Pasteur* began to study the fermentation of TA, he was already in the midst of investigations of lactic and alcoholic fermentations. What, then, prompted him to also examine the fermentation of TA? Some of his biographers have stated that it was the result of a chance discovery: an impure aqueous solution of (+)-TA (or a salt thereof) abandoned on a bench in *Pasteur*'s laboratory for a period of time in warm weather became turbid, a telltale sign of fermentation [81]. It had long been known that solutions of the calcium salt of (+)-TA would ferment under such conditions, and, therefore, according to this account, most other investigators would have thrown out the spoiled tartrate solution without giving it another thought. *Pasteur*, on the other hand, had the insight to consider the implications of this laboratory mishap, and he followed up the accidental observation with imaginative experiments that led to the discovery of biological enantioselectivity [81].

Pasteur, however, did not confirm this serendipitous event in his laboratory, and, in his publications and lectures, he did not mention any such laboratory accident and never portrayed his discovery of the enantioselective tartrate fermentation as the outcome of a chance observation of an accidental fermentation of (+)-TA. For example, in one of his two famous lectures to the Chemical Society of Paris in 1860 he said the following [82]:

'*It had been known for a long time, from an observation by a manufacturer of chemical products in Germany, that impure commercial calcium tartrate* [*i.e.*, calcium

(+)-tartrate], *contaminated with material from live organisms and abandoned in water in the summer, could ferment and produce various products.*

With that established, I carried out the fermentation of ordinary tartrate [*i.e.*, a salt of (+)-TA] *in the following manner* [here *Pasteur* gave the experimental details; they will be omitted in the present recounting]:

So far, nothing unusual, it is a tartrate [*i.e.*, (+)-tartrate] *that ferments. It is a known fact.*

But let us apply this method of fermentation to ammonium paratartrate …'

Similarly, in his memoir [41a] of March, 1858, on the tartrate fermentations, he did not refer to a laboratory accident as the triggering event of those studies. *Pasteur*'s implications are clear: he had been aware of the earlier observations on the spontaneous fermentation of impure (+)-tartrate, confirmed it in his laboratory, and then applied it to (±)-TA. There is no hint of serendipity in his account, which obviously differs from the version given by some of *Pasteur*'s biographers who specifically describe an initial *chance* observation in his laboratory as the trigger for these studies [81]. In this regard, it is noteworthy that *Pasteur* believed that serendipity in scientific discoveries did not have a significant role to play [42].

When and where were the experiments on the fermentation of TA carried out? In this matter also, contradictory information has appeared in the literature. In *La Vie de Pasteur*, *Pasteur*'s biography by his son-in-law *René Vallery-Radot*, the experiments in question are said to have taken place during a period which appears to correspond to late 1853 or early 1854, while *Pasteur* was still in Strasbourg, but no documentation or supporting information is provided by the author for this claim [83]. In his first volume [84] on *Pasteur*, published in 1950, *Dubos* is conflicted on the date of the tartrate-fermentation experiments: on p. 41, he gives 1854 as the period in question and indicates that *Pasteur* was still in Strasbourg at the time, whereas on pp. 106–107 the year is given as 1857.

Several credible sources in fact agree that the experiments were carried out in 1857. In his second work on *Pasteur* ten years after the first volume, *Dubos* settles on 1857 as the period of the tartrate-fermentation work [85]. *L. Pasteur Valery-Radot* stated on the basis of *Pasteur*'s laboratory notebooks that *Pasteur* began his investigations of the fermentation of (+)-TA in April of 1857, and that on August 27 of that year the first experiments on the fermentation of paratartaric acid were undertaken [86]. Moreover, in a letter dated September 7, 1857, *Pasteur* announced to *Biot* his new finding on the enantioselective fermentation of (±)-TA, stating, after a brief summary of the results: '*These are the facts that I wished to notify you of, as soon as they were beyond doubt …*' [87].

It seems clear, therefore, that *a*) the tartrate-fermentation experiments were carried out in 1857, and that *b*) while the memoir of December, 1857, was presented after *Pasteur*'s appointment to the ENS in Paris, the key experiments were performed in Lille, before he moved to Paris.

Pasteur did not identify a specific microorganism in the memoir on the fermentation of TA, although he referred to the organism as a 'yeast' [41a][42]. He also described it as resembling the lactic ferment, *i.e.*, the microorganism he had identified as responsible for lactic acid fermentation. In his scientific biography of *Pasteur*, *Duclaux* suggested that the microorganism of the tartrate fermentation may have been a species

of *Penicillium,* a fungal microorganism [88]. In fact, in 1860 *Pasteur* reported in a brief note that *Penicillium glaucum,* a common mold, enantioselectively metabolized paratartaric acid in a manner very similar to the earlier fermentation: here too, (+)-TA was consumed and (−)-TA was left behind largely untouched [89].

The nature of the products of the fermentation of TA was not addressed by *Pasteur* in his memoir of March, 1858 [41a][42]. He indicated in the memoir that he would soon publish information on this matter, but no such publication ever appeared. He did mention in the memoir an earlier report from the literature that identified *metacetonic acid* as a product of the fermentation of calcium (+)-tartrate. '*Metacetonic acid*' is an old name for propionic acid [90].

No indication is given in the memoir [41a] of March, 1858, whether (−)-TA was separately incubated under the conditions of the fermentation, although the brief statement in the first report (of December, 1857) [41b] suggests that such an experiment had in fact been carried out (see above) [42]. In a related matter, in 1853 *Pasteur* had discovered the racemization of TA when he heated (+)-TA with a cinchona alkaloid, *e.g.*, cinchonidine or quinine. Among the products of the reaction, he found not only (±)-TA but also *meso*-TA (*Fig. 3*), and recognized that this molecule was inherently achiral and that, therefore, the substance was non-resolvable [91]. Interestingly, however, he did not include the *meso*-acid in the investigation of the tartrate fermentation. This is surprising indeed, inasmuch as *Pasteur* recognized and emphasized the importance of the role of chirality as a modifier of affinity in biology [92].

Also relevant in this context is that in 1863 *Pasteur* reported that an anaerobic microorganism fermented calcium (+)-tartrate, and he stated that the behavior of the other TA stereoisomers (he listed them: '*left, inactive* [*i.e.*, *meso*-TA], *and para-tartaric*') under the same conditions would be described in a subsequent memoir [93]. However, no such investigation was published by *Pasteur*, and no documents relating to such a study among *Pasteur*'s unpublished papers were published by *L. Pasteur Valery-Radot* [40].

4.5. *The Impact of* Pasteur*'s Discovery.* The 1860 note [89] on the action of *Penicillium glaucum* on the tartrates was *Pasteur*'s last published investigation of enantioselective fermentations. Thus, the tartrate-fermentation study was but a brief episode in the midst of his first studies of lactic and alcoholic fermentations. Nevertheless, the tartrate-fermentation work caught the attention of the scientific establishment. The Prize for Experimental Physiology for 1859 was awarded by the *Académie* to *Pasteur* for his fermentation studies, and the fermentation of the tartrate isomers was explicitly included in the award statement [94]. Another recognition came in 1861 when he was the winner of the *Jecker* Prize of the Chemistry Section of the *Académie*, and here too, the tartrate-fermentation work was explicitly praised [95].

Pasteur's discovery of the enantioselective metabolism of TA had a considerable impact on the further development of the field. His finding has often been acclaimed as another ('*Pasteur*'s third') method for resolving racemic mixtures (albeit with the loss of one of the enantiomers) [96], but its significance as a demonstration of the role of chirality in biological phenomena slowly gained attention during the second half of the 19th century. During this period, many studies of the stereochemical course of microbiological reactions were stimulated by *Pasteur*'s tartrate-fermentation work.

These early studies examined TA or other compounds as substrates, and eventually included the monumental work of *Fischer* on the stereoselectivity of enzymatic reactions and his famous 'lock-and-key' model of enzyme–substrate interactions. Among the first reviews of the early microbiological work were those of *Fajans* [97] and *Hirsch* [98]. Later, *Nicolle* pointed out that the methodology available to the early workers was at times unreliable, but it was nevertheless convincingly demonstrated that, depending on the microorganism, the substrate, and the conditions used, the stereochemical course could be in favor of one or the other enantiomer, or displayed no enantioselectivity [99].

Pasteur's explanation in the memoir [41a] of March, 1858, for the observed enantioselectivity in the tartrate fermentations is of considerable historical importance and is also highly relevant for today. He proposed that chiral optically active compounds within the constitution of the microorganism are involved in the utilization of the tartrate molecules as nutrients, and stated the fundamental principle that two enantiomerically related molecules (the tartrate enantiomers in this case) can interact differently with a third chiral molecule (*i.e.*, a constituent of the microorganism), and he explained that the chiral constituent of the microorganism does not '*accommodate*' equally well the left- and right-tartrate molecules. This was the first enunciation of that principle, which is generally accepted today as the basis of enantioselectivity in chemistry, biology, and medicine (*i.e.*, in principle, the diastereoisomeric nature of the interactions of two enantiomerically related molecules with a third chiral molecule) [100]. *Pasteur*'s words, '*we see here the property of molecular dissymmetry possessed by natural materials intervening in a physiological phenomenon as a modifier of affinity*', show a clear recognition of the essence of chirality as a modulator of molecular recognition in biology, as we would put it today.

4.6. Pasteur*'s Enantioselective Tartrate Fermentations: Conclusions. Pasteur*'s discovery of biological enantioselectivity was, first, a confirmation of his exceptional ability to identify new and fundamentally important directions for scientific inquiry, and to design crucial experiments for the testing and development of new ideas. His finding was also a revolutionary observation that pointed the way for early investigations of the potential influence of chirality in biological phenomena. In the final analysis, *Pasteur*'s discovery of the enantioselective tartrate fermentation began a process that, over a period of more than a century, established the fundamental importance of molecular chirality in a variety of fields of biology [101].

5. The Discovery of Enantioselectivity at Biological Receptors. – As discussed above, *Pasteur* discovered biological enantioselectivity in 1857 when he found that the enantiomers of TA are metabolized at different rates by a microorganism. However, nearly 30 years elapsed after *Pasteur*'s discovery before the first report, by Italian chemist *Arnaldo Piutti*, appeared, in 1886, on enantioselectivity at a biological receptor [102]. Receptors are macromolecules on the cell surface and inside the cells, and serve as mediators of the effects of hormones, chemical messengers, and a variety of drugs. It is generally recognized today that receptors are of vital importance in many areas of biology; indeed, receptors constitute one of the most important and most intensively studied phenomena in biology. Moreover, it is known today that enantioselectivity is a commonly seen and important aspect of receptor-mediated biological activity. There-

fore, the earliest observation of enantioselectivity at a receptor is of considerable historical importance.

5.1. Arnaldo Piutti. *Arnaldo Teofilo Pietro Piutti* was born on January 23rd, 1857, in Udine, northeast of Venice. For his university studies, *Piutti* enrolled at the University of Turin to study chemistry. He took courses taught by Professor *Hugo* (*Ugo*) *Schiff* (1834–1915), a chemist (of '*Schiff*'s base' fame) from Germany who spent most of his career in Italy [103]. In 1879, *Schiff* moved to Florence as a professor at an institution of higher education which later became the University of Florence [102b]. He invited *Piutti* to join him as his assistant. *Piutti* spent the period 1881–1886 in Florence with *Schiff* [102b].

In 1886, *Piutti* was appointed professor of pharmaceutical chemistry at the University of Sassari, on the island of Sardinia, Italy, but he spent only two years there, leaving in 1888 to occupy the chair of pharmaceutical chemistry at the University of

Fig. 5. Arnaldo Piutti *in the laboratory.* Image and permission to reproduce kindly provided by *Claudia Piutti* and *Pietro* and *Caterina Piutti*.

Naples, a position he held until 1923, when he was appointed to the chair of organic chemistry at the same university [102b]. *Fig. 5* shows *Piutti* as professor at Naples, aged *ca.* 40–50, in the laboratory.

Piutti's most important and lasting work concerned asparagine which will be discussed in detail below. In addition, however, over his career *Piutti* dealt with a surprisingly broad variety of research topics that included a range of organic compounds and reactions, pharmaceuticals, alimentary products, radioactivity, noble gases, lipases, the teaching of chemistry, the composition of mineral waters, atomic-weight determinations, inorganic analysis, inorganic reactions, absorption spectroscopy of organic compounds and inorganic complexes, natural products, *etc.*

Piutti was the recipient of many honors and tributes. For example, in 1922 he became '*socio nazionale*' (*i.e.*, national, full-fledged, member) of the *Accademia dei Lincei* (literally: Academy of the lynx-eyed; also known as Lincean Academy), the prestigious academy of sciences in Italy established in 1603. He was also corresponding member of the *Reale Accademia delle Scienze di Torino* (Royal Academy of Sciences of Turin) and member of many other Italian and foreign scientific societies. *Piutti* died in Conegliano, Italy, on October 19, 1928 [102b][104].

5.2. *Asparagine.* L-Asparagine, a non-essential amino acid (*Fig. 6*), is thought to have been the first amino acid identified in natural sources and was first isolated in 1806 by the renowned French chemist and pharmacist *Louis Nicolas Vauquelin* (1763–1829) and his young assistant *Pierre Jean Robiquet* (1780–1840) [105] (later a respected chemist and pharmacist in his own right). *Vauquelin* and *Robiquet* obtained the substance from the juice of the asparagus plant they indicated to be *Asparagus sativus* L. (L-asparagine is now known to occur in the free state in many other plants as well, *e.g.*, marshmallows, vetches, soybeans, and white lupini beans.).

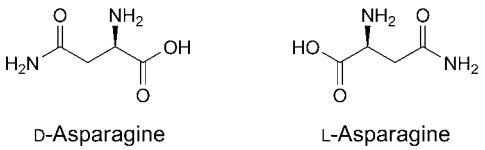

Fig. 6. D- *and* L-*asparagine*

In 1851, *Pasteur* studied the crystals of 'asparagine' (*i.e.*, those of L-asparagine) in great detail and identified their hemihedral nature and recognized their chiral crystal habit [106]. *Fig. 7* shows *Pasteur*'s own drawing of a crystal of asparagine. He also showed that this asparagine was levorotatory in water and in alkaline solutions but dextrorotatory in acidic solutions (he continued to refer to the substance as levorotatory, a convention followed in the present article). *Pasteur* explicitly recognized the chiral nature of the molecules of asparagine (as distinct from the chiral morphology of the asparagine crystals) [106]. It should be noted that at the time of *Pasteur*'s studies an understanding of the nature of chemical structure was still in the future and thus the chemical structure of asparagine was unknown. (−)-L-Asparagine has the (*S*)-configuration (*Fig. 6*).

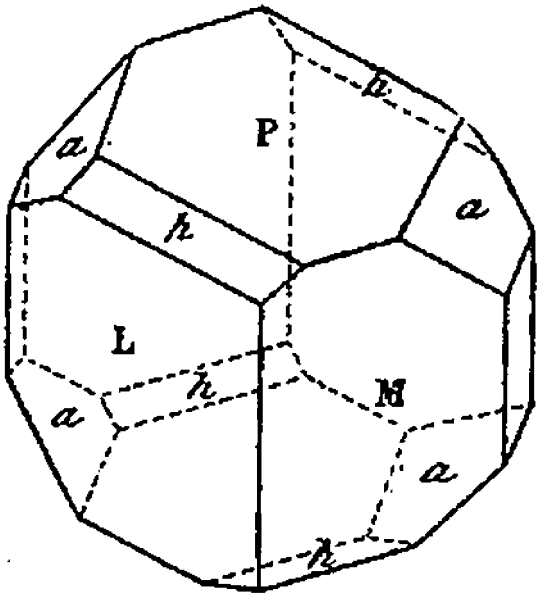

Fig. 7. L-*Asparagine crystal drawn by* Pasteur (reprinted from [106])

5.3. Piutti *Isolates a New Asparagine. Piutti* recounts that in the spring of 1885 he assisted in the production on a large scale of L-asparagine in a factory in Siena [102a]. From 6,500 kg of germinated vetch, 20 kg of crude levorotatory asparagine was obtained. The mother liquors remaining after this operation deposited, with time and natural evaporation, a mixture of two enantiomorphous crystal types, one being L-asparagine and the other a new species. *Piutti* manually separated the crystals and purified the material, obtaining in this manner 100 g of a substance whose crystals were enantiomorphous with the crystal habit of natural (L) asparagine. The optical rotation of the new substance was found to be equal in absolute magnitude and opposite in direction to that of natural asparagine. In addition, the chemical properties and elemental composition of the new compound were the same as those of L-asparagine. *Piutti* wondered whether his new substance was '*physically isomeric*' with or, alternatively, a '*chemical isomer*' of the known '*ordinary*' asparagine. The term '*physical isomer*' was used at the time to refer to what would be called stereoisomer today (and it often referred to chiral substances). It is also clear from *Piutti*'s text that he used '*chemical isomer*' in the sense of today's constitutional isomer. The chemical structure of asparagine was known in its major features at the time but not in all of its details [102b]. Specifically, the presence of the amino, carboxy, and carboxamide groups was known, and it was understood that the latter two were separated by two saturated C-atoms. However, the position of the amino group was uncertain, *i.e.*, it was not known whether the amino group is located α to the carboxy group or α to the carboxamide function. Accordingly, *Piutti* posed the question whether the chemical structures of the two asparagines (*i.e.*, the '*ordinary*' form and his newly isolated

compound) could be '*chemical isomers*', *i.e.*, differing in their constitution insofar as the position of the amino group is concerned, namely, that one of the two substances would have the structure $HO_2CCH(NH_2)CH_2CONH_2$ while the other would correspond to $HOOCCH_2CH(NH_2)CONH_2$. In his historic 1874 pamphlet proposing the tetrahedral C-atom as the explanation for molecular chirality and the consequent optical activity, the Dutch chemist *Jacobus Henricus van't Hoff* (1852–1911) gave the structure of asparagine as $H_2NC(=O)CH_2CH(NH_2)COOH$, *i.e.*, the structure accepted today as correct, with the amino group α to the carboxy group, but he did not cite a source for the structure [48]. On the other hand, in 1875 the French chemist *Édouard Grimaux* (1835–1900) proposed $HOOCCH_2CH(NH_2)CONH_2$ as the structure of asparagine, *i.e.*, with the amino group in the other possible position, that is, α to the carboxamide group [107]. Not surprisingly, then, even as late as 1888, a standard dictionary of chemistry gave '*$CO_2H.CH_2.CH(NH_2).CO.NH_2$ or $CONH_2.CH_2CH(NH_2).CO_2H$*' for the structure of asparagine, *i.e.*, the position of the amino group was still considered uncertain [108].

Piutti, therefore, undertook a synthesis of asparagine with the purpose of determining which of the two constitutional isomers corresponded to the structure of asparagine, and he published the results in 1888 [109]. Using an imaginative synthetic pathway, he showed that asparagine has the α-amino acid structure, and established that his newly isolated form was the mirror-image isomer of natural asparagine [109]. Thus, *Piutti*'s newly isolated compound was D-asparagine (*Fig. 6*). *Piutti* also showed that the isolation of D-asparagine from plants was not the result of the racemization of L-asparagine [110].

5.4. Piutti *Discovers Enantioselectivity in the Taste of the Asparagines.* Even during the isolation and purification process leading to the new asparagine, *Piutti* noticed that the mixture of the two asparagines tasted sweet. The pure D-asparagine he obtained had an intensely sweet taste and in this differed drastically from L-asparagine, which was without taste [102a] (*Vauquelin* and *Robiquet* described the taste of L-asparagine as 'unpleasant' [105]). *Piutti* pointed out that other known amidated acids have a sweet taste, and, importantly, he emphasized that in other known examples of enantiomerically related substances the taste does not differ [102a]. Thus, the discovery of the taste of D-asparagine *vs.* that of the L enantiomer was the first example of a difference in taste found for enantiomerically related substances (indeed, for any stereoisomerically related substances). In hindsight, it was also the discovery of the first example of enantioselectivity at a biological (human) receptor, the sweetness receptor [102b]. It should be pointed out in this regard, however, that the concept of receptors was first proposed only *ca.* 15 years after *Piutti*'s discovery, by the German physician and immunologist *Paul Ehrlich* (1854–1915) and, independently, by the British physiologist *John Newport Langley* (1852–1925) [111].

The first human receptor for sweet taste, a class C heterodimeric G-protein-coupled receptor, was identified recently [112]. Since its discovery, a great deal of work has been devoted to its various aspects, including ligand binding, receptor structure, signal transduction mechanisms, *etc.*, and, as a result, considerable progress has been achieved in this field. However, much remains to be elucidated about the details of the interactions of chiral sweet molecules with the receptor [102b].

In conclusion, *Piutti*'s discovery of a difference in the taste of D- and L-asparagine was a milestone first observation of enantioselectivity at a biological (human) receptor. The discovery was also the first observation of stereoselectivity of any kind in taste, the first finding of biological enantioselectivity in an organism higher than microorganisms, the first example of biological enantioselectivity in an effect other than enzyme action, and one of the two earliest reports of the preparation of a D-amino acid. *Piutti* also established the structure of asparagine with an elegant synthetic pathway and showed that D-asparagine occurs naturally by demonstrating that its isolation can be carried out without any racemization of L-asparagine which is also present in the plants. The announcement of *Piutti*'s discovery in 1886 soon stimulated additional studies by others and elicited recognition from eminent scientists [102b].

6. Chirality in Drugs: A Historical View. – Arguably, a great deal of the intense interest today in the chemical and biological aspects of molecular chirality is driven by the importance of the phenomenon in pharmacotherapy and new-drug development. Therefore, in an article on the historical aspects of molecular chirality, the history of chiral drugs is of relevance [101d].

Chiral molecules are the constituents of a large portion of therapeutic agents. In 1984, *Simonyi* surveyed a Swedish manual of drugs in clinical use and found that of a total of 666 drugs 355 (53%) had at least one stereogenic center; 181 drugs (27% of the total) were in use in single-enantiomer form, while 174 (26%) were racemic [101b]. In 1987 *Ariens* and *Wuis* estimated that *ca.* 57% of marketed drugs are chiral (*i.e.*, drugs based on chiral molecules, be they single enantiomers, racemic mixtures, or some other combinations of chiral stereoisomers) [113]. They also showed that *ca.* 55% of the chiral drugs were used clinically in racemic form and the remainder as single enantiomers. Overall it appears, therefore, that by the end of the 20th century about half of the chiral drugs were single enantiomers and the other half racemic [113].

6.1. *Old Chiral Drugs: Natural Remedies 3000 BCE–1900*. For thousands of years, remedies from nature obtained from vegetable, animal, or mineral sources were relied upon for relief from human diseases. Such folk medicine was by its very nature inaccurate and unscientific, and often had no rational basis. Moreover, toxicity of many of the products was a serious problem; indeed, some of the pharmacologically active preparations were used as poisons. The advent of the printing press in the 15th century resulted in the wide dissemination of knowledge about natural medications, and this in turn produced a considerable increase in the use, and misuse, of such remedies [114]. More rational therapy with purified natural products did not begin until the 1800s.

Despite the problems, however, some of the natural preparations were effective in relieving the symptoms and at times even eliminating the disease. In fact, we know today that the number of pharmacologically active substances produced by nature is large, and the spectrum of biological activities of natural products is extraordinarily broad.

Chirality is a hallmark of many molecules from nature. Indeed, the number of chiral natural molecules is very large, and the structural variety they represent is vast. Among such substances – be they small molecules or macromolecules – an overwhelming majority occur in single-enantiomer form. For example, chiral α-amino acids, and the peptides and proteins containing them, sugars and their polysaccharides, steroids, many

antibiotics, and a large variety of other compounds from nature are single enantiomers. Another important aspect of many chiral molecules from nature concerns their sense of chirality. That is, closely related chiral molecules in the same chemical class usually have the same sense of chirality, *i.e.*, same actual spatial configuration. For example, with relatively few exceptions α-amino acids occurring in nature consistently have the L-configuration; similarly, monosaccharides are of the D-configuration (a note of caution: in some cases, two related molecules of the same configuration may have differing *Cahn–Ingold–Prelog* descriptors; for example, (*S*)-alanine and (*R*)-cysteine have the same (L) absolute configuration. This is, of course, the result of the particular identity of the substituents around the stereogenic center). Thus, both *single-enantiomer* character and *configurational identity* are typical for compounds from nature, that is, most of them occur in single-enantiomer form, and closely related molecules usually have the same sense of chirality.

In light of the above, then, it is not surprising that many of the compounds used as therapeutic agents in natural remedies over the centuries and millennia have been chiral, and that the vast majority of such substances occur in single-enantiomer form. For thousands of years and until the beginning of the 19th century, most such natural remedies were used as crude plant extracts rather than purified active principles. Obviously, in that 'pre-scientific' era, the remedies were used without any knowledge as to the nature or identity of the active ingredient(s) within, let alone any understanding of the chirality of the molecules involved. Recognition of the existence of chiral drugs had to await a better understanding of chemical structure, *i.e.*, the advent of modern organic chemistry and the discovery of molecular chirality.

Information about some of the earliest herbal remedies that contain chiral active ingredients goes back nearly 5000 years. A few examples of old therapies with chiral active ingredients are presented below.

6.1.1. Shen Nung *and Old Chinese Drugs.* In a book about herbs, the Chinese scholar-emperor *Shen Nung* described in 2735 BCE the beneficial effects of *Ch'ang Shan* in the treatment of 'fevers' [115]. This preparation is the powdered root of a plant, *Dichroa febrifuga* LOUR. Modern medicinal chemistry has identified several alkaloids with *antimalarial* properties in the plant, and it is, therefore, clear that the ancient use of *Ch'ang Shan* in fevers was not entirely without basis. One of the antimalarial compounds from *Ch'ang Shan* is *februgine* (β-dichroine), a relatively simple single-enantiomer compound (*Fig. 8*). Modern attempts to develop these agents as antimalarial drugs failed, due to significant toxicity [115].

Shen Nung also observed the stimulant properties of another Chinese plant, *Ma Huang*, now known as *Ephedra sinica* [116]. The chief active ingredient, *ephedrine,* is a sympathomimetic amine, and, therefore, it is clear in this case also that the medicinal use of *Ma Huang* as a stimulant had a rational basis. The ephedrine molecule is simple and contains two stereogenic C-centers; the compound from *ephedra* is the levorotatory single-enantiomer and of (1*R*,2*S*)-configuration (*Fig. 8*). Ephedrine was first isolated from *Ma Huang* in 1887 [117], *i.e.*, more than 4,600 years after the effects of the compound were recorded. Ephedrine was introduced into medical practice during the 1920s [118] and for decades was widely used – as a CNS stimulant in narcolepsy, as a bronchodilator, in the treatment of *Adams–Stokes* syndrome with complete heart block, as a stimulant in some forms of depression, and in some other

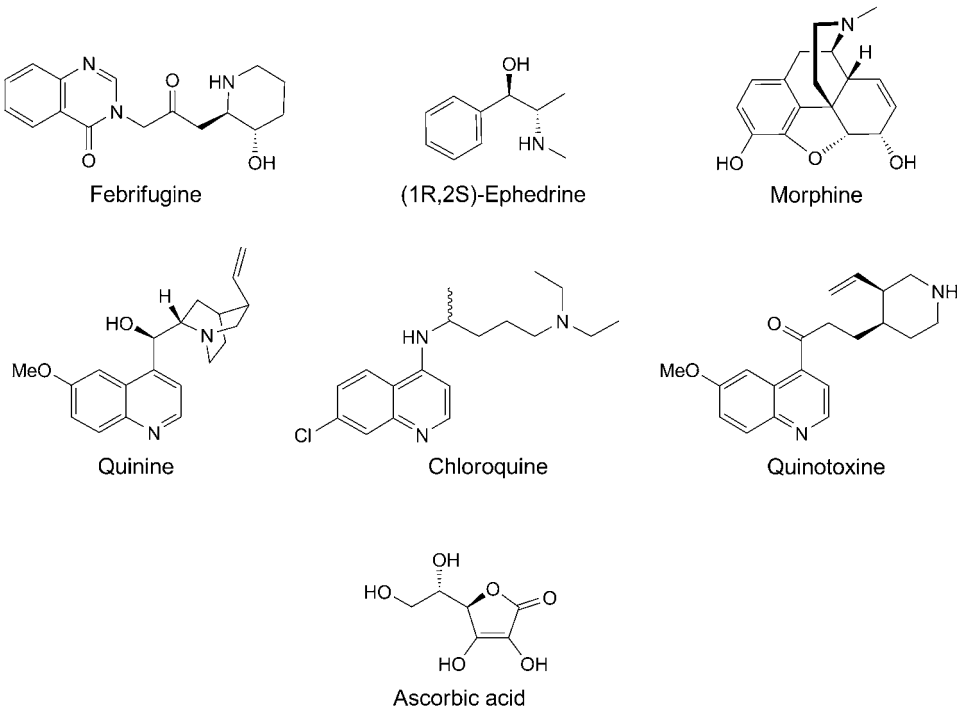

Fig. 8. *Structures of some of the old chiral drugs discussed in the text*

disorders. However, more recently ephedrine has been largely replaced in most of these indications by other treatment modalities [119]. Ephedrine has also been widely available in 'dietary supplements' for weight loss, increased energy, body building, *etc.* However, in the early 1990s concern arose over potentially serious adverse effects from such use of ephedrine, including cardiovascular, nervous-system, and other toxic effects, and in April 2004 the U.S. Food and Drug Administration (FDA) banned the sale in the United States of dietary supplements containing ephedrine or closely related compounds [120].

6.1.2. *Morphine.* Another millennia-old single-enantiomer drug is the opioid agent morphine. *Opioid* refers broadly to all compounds related to opium (a more recent definition states that the term *opioid* includes any compound that interacts with the brain's opioid receptors [121]). Opium powder is the dried juice from the unripe seed capsule of the poppy *Papaver somniferum*, and its name is derived from the diminutive of the Greek word *opos*, *i.e.*, juice. Opium has analgesic, euphoric, and other effects, and contains many alkaloids, including morphine and codeine. Poppy juice is mentioned in the writings of the Greek philosopher and naturalist *Theophrastus* (*ca.* 371 – 287 BCE), but evidence has been found suggesting that opium may have been known much earlier to ancient civilizations in Egypt and Mesopotamia [121][122]. Within the Arab-Islamic civilization, whose rise began in the 7th century, opium came to be used mainly as a constipant to control dysentery [123]. The arrival of the Islamic

armies and influence in Europe in the 16th century (Constantinople fell to the Ottoman Turks in 1453, and the first siege of Vienna by the Ottoman army took place in 1529) brought opium to Europe. *Laudanum*, a somewhat purified opium concentrate, was compounded by *Paracelsus* (*Theophrastus Bombastus von Hohenheim*, 1493 – 1541), a Swiss alchemist and physician, and the smoking of opium became openly popular during the 1700s; however, opium may have been extensively but less openly used in Europe in earlier times [124].

Morphine, the most important alkaloid in opium, was obtained as a purified powder from opium around 1805 by *Friedrich Wilhelm Sertürner* (1783 – 1841), a German pharmacist's assistant [125]. He named it *morphium* after *Morpheus*, the Latin god of dreams named by *Ovid* using a Greek word. Natural morphine is levorotatory and has the pentacyclic tertiary-amine structure with five stereogenic centers (*Fig. 8*).

The invention of the hypodermic needle and syringe in the middle of the 19th century resulted in the widespread use of morphine, and addiction became a common problem. An early – and false – hope to circumvent the addiction liability of morphine was provided by a most unlikely candidate: heroin. This compound, the diacetyl derivative of morphine, is a potent opiate narcotic first synthesized in 1874 *via* acetylation of morphine, and was introduced into medical practice in 1898 as a cough suppressant [123]. Heroin is a *semisynthetic* drug, *i.e.*, a chemically modified derivative of a natural product, and retains the configuration of morphine. Heroin may have been the first synthetic single-enantiomer drug introduced in clinical medicine.

Heroin was actively marketed to physicians by its manufacturer. The drug was touted as a 'non-addicting' morphine analog that could safely replace morphine and thereby eliminate the latter's addiction problem [126]. This claim turned out to be tragically mistaken, and today heroin is a highly abused opioid, with grave social, economic, and medical consequences.

6.1.3. *Quinine.* The earliest history of quinine is obscure, but it is known that by the first decades of the 17th century the substance was being used, as a crude extract of the bark of the *cinchona* tree (*Fig. 9*), for the treatment of malaria by South American natives in Peru, Ecuador, and neighboring regions [128]. In 1633, *Antonio de la Calancha* (1584 – 1654), an Augustinian monk in Lima, wrote a pamphlet describing the native use and fever-curing powers of cinchona [129], and by the middle of 1600s the extract of 'Jesuit's bark' (one of the names cinchona came to be known by) was being used in Europe indiscriminately for a variety of fevers. Cinchona was, however, effective only against malaria, an infectious disease widespread in many parts of the world, including Africa, Asia, and, until relatively recently, even in Europe and North America. Cinchona was the first effective treatment for malaria, and in 1820 the French pharmacists *Pierre Joseph Pelletier* (1788 – 1842) and *Joseph Bienaimé Caventou* (1795 – 1877) isolated quinine, the main antimalarial ingredient, from cinchona bark [130].

The quinine molecule contains four stereogenic C-centers (*Fig. 8*) and the natural compound is levorotatory. The name *quinine,* given by *Pelletier* and *Caventou* to their new substance [130], is derived from *quina quina* ('bark of barks'), the Spanish spelling of a native Quechua name that was sometimes used for the cinchona bark in Peru.

After its isolation in 1820, purified quinine quickly replaced the crude cinchona preparations in the treatment of malaria. Supplies of quinine were limited, and the need

Fig. 9. *One of the earliest illustrations of the cinchona tree, from* Jonston's Dendrographias*, published in 1662*. Reprinted from [127].

was great, as the drug was in demand for the treatment of malaria not only in Europe but also in various parts of Africa, Asia, and Latin America, where European powers were engaged in establishing or strengthening their colonial control. Therefore, the synthesis of quinine became an attractive idea to chemists in Europe. In England in 1856 an 18-year-old chemistry student named *William Henry Perkin* (1838–1907), working with *August Wilhelm von Hofmann* (1818–1892), a German professor of

chemistry appointed director of the newly established Royal College of Chemistry in London, attempted to synthesize quinine by oxidizing *N*-allyltoluidine with potassium dichromate. The reaction, predictably in hindsight, did not produce quinine, but *Perkin*'s further studies of the reaction led to the discovery of *mauveine*, a purple dye which in turn launched the artificial, 'aniline' or 'coal-tar', dye industry. The invention of mauveine not only revolutionized the dye and textile industries but also produced an intense stimulatory effect on chemical research in general, on the pharmaceutical industry, and on medicine [131] (*Perkin*'s mauveine is a mixture of several phenazine derivatives, none of which is chiral).

The synthesis of quinine has had an interesting and controversial history [132]. The first total synthesis was claimed by *Woodward* and *Doering* during World War II [133]. At the time, the Allies were suffering from a severe shortage of quinine, which was needed for Allied troops fighting in malarious regions. The shortage was the result of the fact that large-scale cultivation of cinchona had by then shifted primarily to Java, then a Dutch colony (now part of Indonesia) occupied by Japan during the war. The announcement of the *Woodward–Doering* synthesis was, therefore, enthusiastically received by the lay press, due in part to the belief that the synthesis represented a potential solution to the quinine shortage. However, such hopes were unjustified, since the synthesis, while clearly an important scientific achievement, was nevertheless much too complex and inefficient to have any potential for the industrial production of quinine.

In the synthetic sequence [133], *Woodward* and *Doering* stopped at (+)-quinotoxine (*Fig. 8*), a compound whose conversion to quinine in three steps had been claimed in 1918 by *Rabe* and *Kindler* [134]. Thus, *Woodward* and *Doering* stated that they had achieved the *formal* total synthesis of quinine. However, their work was criticized by *Stork* [132b][135] as not a valid formal total synthesis, for several reasons. First, it was said that the experimental details of the conversion of (+)-quinotoxine to quinine had not been provided by *Rabe* and *Kindler* in their 1918 paper; in addition, it was pointed out that the *Woodward–Doering* synthesis lacked stereospecificity [135]. In 2001, *Stork et al.* published their own synthesis which provided quinine readily isolated as the single stereoisomer [135]. This controversy around the *Woodward–Doering* synthesis received considerable attention, and the issue was analyzed in detail by the respected historian of chemistry *Jeffrey Seeman* [132b]. On the basis of information obtained from a variety of published and archival sources, *Seeman* made a convincing case that the synthesis by *Woodward* and *Doering* was in fact a valid formal total synthesis [132b]. Subsequently, *Smith* and *Williams* [136] successfully duplicated the conversion of (+)-quinotoxine to quinine (which was obtained as an analytically pure sample) as reported by *Rabe* and *Kindler*, and using only techniques available to *Rabe–Kindler* in 1918 and to *Woodward–Doering* in 1944. Thus, *Smith* and *Williams* experimentally validated the claim by *Woodward* and *Doering* of the formal total synthesis of quinine, and also confirmed *Seeman*'s conclusions [132b] concerning the synthesis.

Later, additional syntheses of quinine also appeared [132a][137], but it is noteworthy that the commercial production of the substance remains based on its isolation from cinchona, since the published syntheses are unsuitable for large-scale commercial production.

The need for effective antimalarial drugs has persisted over the nearly two centuries since quinine was first isolated. Modifications of the quinine molecule have produced many initially useful antimalarial agents, including the chiral drugs quinacrine, primaquine, and chloroquine. These compounds were introduced during the 20th century, in racemic form. Chloroquine (*Fig. 8*; preparation patent issued 1939) was particularly useful inasmuch as it was cheap, easy to use, and effective, but resistance by the malaria parasites to this drug (and several related agents) has rendered it ineffective in most parts of the world where the disease is endemic [138]. Malaria remains one of the great killer diseases: '*in 2010, malaria caused an estimated 660,000 deaths (with an uncertainty range of 490,000 to 836,000), mostly among African children*' [139].

6.1.4. *Ascorbic Acid.* The devastating disease scurvy is caused by insufficient amounts of L-ascorbic acid (vitamin C; *Fig. 8*) in the diet. After the 15th century, exploration, expanding trade, and colonization by European powers required long sea voyages, usually undertaken without foods rich in vitamin C on board. The result was the decimation of ships' crews by scurvy. In a remarkable study in 1747 that can be described as the first serious clinical therapeutic trial, British physician *James Lind* (1716–1794), a surgeon in the Royal Navy and the '*father of naval hygiene*', demonstrated that fruits such as oranges and lemons can reverse and prevent the disease. However, it took nearly 50 years for the British Admiralty to take notice of these findings and institute, in 1795, an appropriate diet on board Royal Navy ships to prevent scurvy [140].

Hungarian biochemist *Albert Szent-Györgyi* (1893–1986) isolated vitamin C from fruit juices in 1932 [141], and in part for this work he was awarded the *Nobel* Prize in Physiology or Medicine in 1937. In that same year, one half of the *Nobel* Prize in Chemistry went to the English chemist *Walter Norman Haworth* (1883–1950) for the proof of structure and synthesis of ascorbic acid [142].

6.1.5. *Old Chiral Drugs: Final Comments.* The above examples of old chiral drugs from natural sources are but a handful from a long list of such substances. A few additional examples can be mentioned (some plant origins given in parentheses): tetrahydrocannabinol (marihuana; hashish), digoxin (foxglove; *Digitalis lanata* EHRH.), cocaine (*Erythroxylon*), cathinone (khat, *Catha edulis* FORSK.), nicotine (tobacco, *Nicotiana tabacum*), atropine (deadly nightshade, *Atropa belladonna* L.), reserpine (*Rauwolfia*), colchicine (autumn crocus, meadow saffron), and emetine (ipecac), *etc.*

The vast majority of chiral drugs present in the old remedies were single-enantiomer substances: Mother Nature is not even-handed. All in all, chiral drugs have been of great importance in the development of pharmacotherapy, from the earliest plant remedies of millennia ago to the modern age. Many of these ancient chiral drugs are still in use today, and many new and important drugs have been developed by modifying the molecules of natural products identified in old remedies.

6.2. *The First Recognition of Chirality in Drugs.* The first steps on the road to the full appreciation of chirality in therapeutic agents were taken by *Pasteur*. Strictly speaking, his discovery of the chiral nature of the molecules of TA may be considered the first recognition of the chirality of a drug, since (+)-TA (as its antimony potassium salt) was in use at the time as an emetic ('*tartar emetic*'). Perhaps more significantly in the

present context, in the early 1850s *Pasteur* studied many other chiral compounds, including quinine, which was widely used as an antimalarial agent at the time. He recognized that the molecules of quinine were chiral, and that the substance isolated from its natural source was a single enantiomer, and he measured its optical rotation and described its crystal habit [143]. He also recognized the chirality of some other therapeutic agents, *e.g.*, morphine, whose crystals he studied [144], and camphor [145]. Clearly, *Pasteur* was the first to realize, in the middle of the 19th century, that the molecules of certain therapeutic agents are chiral.

6.3. *Drug Chirality in the 20th Century.* The 'pre-science' era of pharmacotherapy based on crude natural remedies came to an end as the 19th century was winding down. As organic chemistry advanced, the veil was slowly lifting from the mystery of chemical structures. Many natural products were now purified from their sources and their chemical structures were (sooner or later) elucidated. With time, many synthetic therapeutic agents were also introduced, and many of these were chiral.

These developments in turn led to the increasing availability of both enantiomeric forms of many chiral drugs which then permitted studies comparing the enantiomers for their pharmacological actions and biological fate. During the 20th century, many such studies were carried out and enantioselectivity in drug action and disposition was often found. To mention only a few examples, in 1920 (−)-hyoscyamine (*Fig. 10*) was found to be *ca.* 12–20 times more potent than the *dextro*-enantiomer in a variety of physiological or pharmacological effects, *e.g.*, mydriasis in the cat, salivary secretion in the dog, and at cardiac myoneural junctions, but, interestingly, (+)-hyoscyamine was the more potent enantiomer in CNS-excitatory effects [146]; in 1940, significant biological differences between the enantiomers of sex hormones, *e.g.*, those of the steroid equilenin (*Fig. 10*), were reported [147]; natural (−)-morphine was synthesized in 1952 [148] and its absolute configuration determined in 1955 [149]; (+)-morphine was synthesized in 1960 and was shown to differ significantly from (−)-morphine in that the former was found to lack analgesic activity [150]; the β-adrenergic-antagonist activity of propranolol (*Fig. 10*), the first commercially successful such drug, was determined to be lopsidedly in the (−)-(*S*) enantiomer, and a similar dependence of the activity on configuration was found in several other, related, 'β-blockers' [151]. Examples of enantioselective toxicity were also found, *e.g.*, for 3,4-dihydroxyphenylalanine. Initial clinical trials in the 1960s of this breakthrough treatment for *Parkinson*'s disease used the racemic mixture but it quickly became clear that unacceptable toxicity was present in the D-enantiomer, and the drug was, therefore, developed in the single-enantiomer L form (levodopa; *Fig. 10*) [152].

In 1933, *Easson* and *Stedman* proposed a fundamental model of molecular interactions as an explanation for an enantioselective pharmacological action [153]. The model was deduced from studies of the pressor (blood-pressure-increasing) effects of the enantiomers of epinephrine which showed a 12–15-fold enantioselectivity, the natural (−)-(*R*) form (*Fig. 10*) being the more potent enantiomer. It was concluded that three groups in the molecule – the amino group, the aliphatic hydroxy group, and the electron-rich aromatic ring – interact with three complementary sites on the (chiral) biological mediator of the action of the drug, and it was argued from the three-dimensional geometry of contact between two chiral entities (the drug and the effector) that, if all three groups of (−)-epinephrine simultaneously fit three complementary

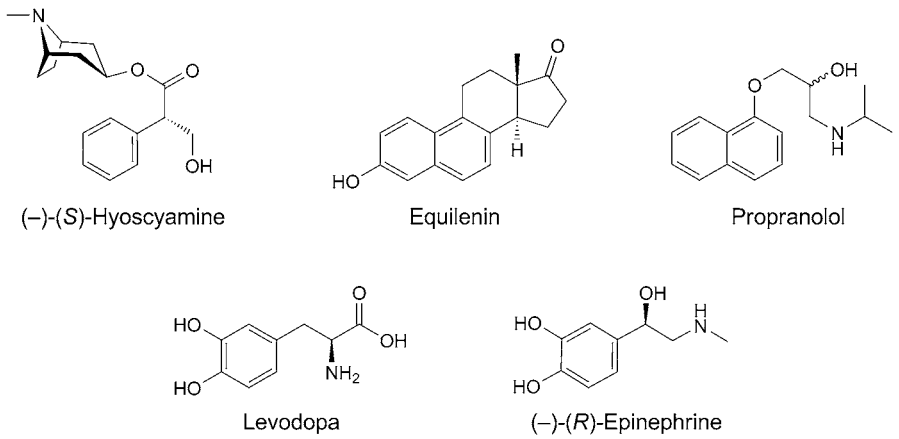

Fig. 10. *Structures of some of the chiral drugs of the 20th century discussed in the text*

sites on the biological mediator, (+)-epinephrine will not be able to interact fully or in the same manner with the same three binding sites on the receptor – in fact, at most only two of the interacting groups of this enantiomer could simultaneously bind to their complementary sites. This differential binding, it was suggested [153], accounts for the differences in the biological effects of the enantiomers. The three-point-interaction model, originally proposed for a specific effect of epinephrine, was later broadened to explain biological enantioselectivity of chiral drugs in general [154], be it in drug receptor interactions, enzyme–substrate interactions, protein binding, *etc.* It is important to recognize that the model is based on purely geometric considerations, and there is nothing inherently biological in it. Indeed, the three-point-interaction model of enantioselectivity has also been used in chromatography to explain enantiomer separations using chiral stationary phases or other chiral selectors [155]. Subsequent investigations have revealed additional complexities in the enantioselectivity of some drug–mediator interactions and, therefore, in some cases reinterpretation of the *Easson–Stedman* model or the introduction of other models has been deemed necessary [156].

Thus, by the end of the 20th century a large body of information had accumulated on the role of chirality in drug action and disposition, and many reviews and monographs on the subject appeared during the last *ca.* three decades of the century [157].

6.4. *Chirality in the Development of New Drugs: Some Recent History.* Surprisingly, the new information on the role of chirality in drug action and disposition accumulated in the 20th century was not rapidly exploited for some of its possible benefits. In particular, the new understanding of the role of chirality did not make a significant impact in the development and marketing of new chiral drugs for many years. Indeed, during a long period the pharmaceutical industry and governmental drug-regulatory authorities did not actively address the implications and potential of molecular chirality for better and safer drugs. This neglect may have had its explanation, at least in part, in the lack of availability, certainly during the first part of the period in question, of

scientific and technical tools essential for the research and development work needed to translate the accumulated scientific information on chirality into better and safer drugs (see below). Thus, the vast majority of synthetic chiral drugs introduced by 1987, *ca.* 88%, were racemic, *i.e.*, the potential advantages (see below) of single-enantiomer drugs were not exploited [101b][113].

It was only in the 1990s that this situation began to change significantly. Thus, in 1992 the FDA was the first drug-regulatory authority to issue guidelines specifically aimed at the development of new drugs based on chiral molecules [158]. Shortly thereafter other drug-regulatory authorities around the world also began to address the issue [159]. The new regulations thus introduced require that during the development of new drugs the role and implications of molecular chirality be taken into account. The impact of this change has been dramatic [160]. For example, today the appearance of a new racemic drug on the market is a rare event, with most new chiral drugs now being introduced in the single-enantiomer form (the significance of this change can be appreciated when we consider that at the time of the publication of the new FDA rules, in 1992, *ca.* 25% of all marketed drugs were racemic). However, the development and marketing of a racemic drug are still justified in several scenarios [159b]. One such justification concerns drugs that are stereochemically labile, *i.e.*, if there is *in vitro* or *in vivo* racemization, or an *in vivo* stereochemical inversion on a time scale sufficiently fast to be relevant to the shelf-life of the drug or to its composition during the therapeutic treatment [161]. A class of drugs where *in vivo* inversion of one of the enantiomers is commonly seen is the '*profens*', *i.e.*, the 2-arylproprionic-acid-based analgesic and anti-inflammatory agents [162]. Other scenarios are also envisaged for the introduction of new racemic drugs [159b], but in practice there has been a relentless trend toward single-enantiomer compounds in the development of new therapeutic agents. The decisions made by pharmaceutical firms concerning the choice of the stereochemical form (single enantiomer or racemate or other mixture) of a new drug candidate are based on both scientific and economic considerations [159b].

Thus, in the 1990s, regulatory authorities and the pharmaceutical industry began to act on the recognition that, in many cases, the two enantiomers in a racemic mixture are two biologically distinctly different substances. In most cases, in fact, the two enantiomers will differ in some aspects of their effects and/or biological fate, and there are many examples where the enantiomers have been found to differ considerably – and at times drastically – in their pharmacology, toxicology, clinical efficacy, and/or pharmacokinetics, *etc.* Overall, it is generally believed today that a single-enantiomer form of a therapeutic agent may well have advantages over the racemic or some other stereoisomer mixture. For example, the pharmacology and toxicology profiles will be clearer for the single substance; the pharmacokinetics, and the relationship between serum concentration and biological effects will be more readily interpretable; in some cases adverse effects or toxicity will be eliminated or reduced with the removal of the less-favorable stereoisomer; the dosage of the single-enantiomer drug may be lower than that of the stereoisomer mixture, *etc.*

However, a word of caution is in order here: in a few cases it has been shown that the racemic or some other mixture of the stereoisomers was a safer drug than a single-enantiomer form [163]. Thus, each case should be considered on its own merits.

The question may be asked: what were the factors that finally produced this change in attitude toward the role of chirality in new-drug development? In retrospect, it appears that advances in two chemical disciplines facilitated, indeed, permitted the recognition of the importance of molecular chirality in new-drug development:

1) The considerable advances in stereoselective synthesis during the last several decades of the 20th century [164]. Such improvements in organic synthesis have allowed the preparation of a wide variety of single-enantiomer drugs, drug metabolites, and related substances, including many with highly complex stereochemistry.

2) The advent, during the same period, of powerful methods for enantioselective analysis, *i.e.*, the detection and quantification of enantiomerically related substances in the presence of each other, particularly *via* enantioselective chromatography [165]. The benefits of such analytical methodology are multifold. For example, the new chromatographic analytical methods have allowed the convenient, rapid, precise, and accurate determination of the enantiomer composition or enantiomeric purity of chiral substances, even in cases of trace contamination of a single-enantiomer compound with the enantiomer. Such enantioselective analytical capability is essential in the preparation of single-enantiomer substances of high stereochemical purity and in the development of the necessary stereoselective synthetic methods; these analytical methods are also required to assure stereochemical purity during pharmacological testing, where even low levels of contamination of the *distomer* (the biologically less potent enantioform) with the *eutomer* (more potent enantiomer) may distort the results; and, of course, the new analytical methodology has also allowed the study of enantioselectivity in the pharmacokinetics and metabolism of chiral substances. (An important additional advantage of some of the enantioselective chromatographic separations is that in the preparative mode they may rapidly provide sufficient amounts of the individual enantiomers for prompt initial pharmacological and toxicological evaluation [165d], without the need to resort to enantioselective syntheses, whose development is often challenging and time-consuming.)

Overall, it is clear that chirality plays an important role in molecular and clinical pharmacology [166], and a strong component of the interest in the role of molecular chirality in chemistry and in biology derives from its significance for pharmacotherapy, the development of new drugs, and the corresponding needs of the pharmaceutical industry. In addition, in a broader sense, it is widely recognized today that the chemical phenomenon of molecular chirality is a fundamentally important modulator of the effects and properties of chiral substances in a variety of branches of biology and medicine [101].

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