Introduction

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1.1 Introduction

Chiral molecules are constituents of a large proportion 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 chiral center; 181 drugs (27% of the total) were in use in single-enantiomer form while 174 (26%) were racemic [1]. In1987 Ariens and Wuis estimated that ca. 57% of marketed drugs are chiral (that is, are based on chiral molecules, be they racemic, single-enantiomeric, or some other mixture of chiral stereoisomers) [2]. They also showed that ca. 55% of the chiral drugs were used clinically in the racemic form and the remainder as single-enantiomers. Overall it appears, therefore, that by the end of the century ca. half of the chiral drugs were single-enantiomeric and the other half racemic.

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The situation is different today. With rare exceptions new chiral drugs are developed in single-enantiomer form, and new racemic drugs are highly unlikely to appear. This is a profound change in drug development from a stereochemical viewpoint. How did we get here? What are the factors that have influenced the introduction and use of therapeutic agents based on chiral molecules? What is the history of chiral drugs?

1.2 A Word About Words

Before we attempt to answer the above questions, we need to examine briefly the terminology relevant to a discussion of chiral drugs. Specifically, the definition and usage of two important terms need to be clarified. *Chiral* was defined in one recent leading monograph on stereochemistry as follows: "Not superposable ... with its mirror image, as applied to molecules, conformations, as well as macroscopic objects, such as crystals" [3]. Mislow gave a shorter but essentially equivalent definition: "An object is chiral if and only if it is not superposable on its mir-

ror image; otherwise it is achiral" [4]. Thus, it is clear that *chiral* refers to a spatial property of objects, including molecules. Therefore, the term describes that nature of a molecule which makes it *non-superposable* on its mirror image, and *does not refer to the stereochemical composition of bulk material, i.e., drugs, compounds, sub-stances, etc.* [5]. Thus, "chiral drug" does not tell us whether the drug is racemic, single-enantiomeric, or some other mixture of the stereoisomers. In the present article, therefore, *chiral* will be used strictly according to the definitions cited above, i.e., to refer to the chirality of individual molecules or other chiral *objects*. Thus, "chiral drug", "chiral substance", etc., will be used to indicate that the drug in question is composed of chiral molecules, but the enantiomer composition is not specified by this terminology.

There is however a great and obvious need for a convenient term to refer to chiral substances that are composed of only one of the two enantiomers. Numerous terms for this purpose have been introduced over many years, but the issue remains complex and largely unresolved. The present author recently discussed this issue in detail and introduced a new term for the purpose: *unichiral* [5]. In the present chapter *unichiral* will be used to specify the stereochemical composition of a chiral drug, substance, compound, sample, etc, as stereochemically homogeneous, i.e., consisting of a single-enantiomer (in the context where the term is used and within the limits of measurement) [5].

1.3 Old Chiral Drugs: Natural Remedies 3000BC-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, the 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 [6]. 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; for example, antimicrobial, antineoplastic, CNS-active, anti-inflammatory, cardiovascular, etc., are only a few of the therapeutic classes of drugs from nature [7].

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 unichiral form. For example, chiral α -amino acids

and the peptides and proteins containing them, sugars and their polysaccharides, steroids, antibiotics, and many other compounds from nature are unichiral. Another important aspect of many chiral molecules from nature is their *homochirality*. This means that related chiral molecules in the same chemical class usually have the same sense of chirality. For example, with rare exceptions α -amino acids occurring in nature consistently have the L configuration; similarly, monosaccharides are of the D configuration. Thus, both *unichirality* and *homochirality* are typical for compounds from nature: most of them occur in enantiomerically homogeneous form, and closely related molecules usually have the same sense of chirality.

In the 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 unichiral 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 clue 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 (see below).

The number of pharmacologically active agents now known to be present in various old remedies is large [7] and many of these compounds are based on chiral molecules. 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.

In a book about herbs, the Chinese scholar-emperor Shen Nung described in 2735 BC the beneficial effects of *Ch'ang Shan* in the treatment of "fevers" [8]. 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 unichiral compound **1**. Modern attempts to develop these agents as antimalarial drugs failed, due to significant toxicity [8].



Shen Nung also observed the stimulant properties of another Chinese plant, Ma Huang, now known as *Ephedra sinica* [9]. The chief active ingredient, *ephedrine*, is a sympathomimetic amine, and therefore it is clear in this case also that the use of Ma Huang as a stimulant had a rational basis. The ephedrine molecule is simple and contains two chiral centers; the compound from *ephedra* is unichiral and has the 1*R*,2*S* configuration **2**. Ephedrine was first isolated from Ma Huang in 1887

[10], i. e., more than 4600 years after the effects of the compound were recorded. Ephedrine was introduced into medical practice during the 1920s [11] 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 disorders – but more recently it has been largely replaced in most of these indications by other treatment modalities [12]. 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 [13].



Another millennia-old unichiral 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) [14]. 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 3 and codeine 4. Poppy juice is mentioned in the writings of the Greek philosopher and naturalist Theophrastus (ca. 371-287 BC), but evidence has been found suggesting that opium may have been known much earlier, to ancient civilizations in Egypt and Mesopotamia (Fig. 1.1) [14, 15]. Within the Arab-Islamic civilization, whose rise began in the 7th century, opium came to be used mainly as a constipant to control dysentery [16]. The arrival of the Islamic armies and their 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 [17].





Fig. 1.1 Frieze from the palace of Assyrian king Sargon II, in Khorsabad (in modern-day Iraq), depicting two priests. Note the poppy heads carried by the priest on the right. 8th century BC. Musée du Louvre, Paris, Antiquités orientales. Photograph: Service de documentation photographique de la Réunion des Musées Nationaux, Château de Versailles. (Reprinted from Lydia Mez-Mangold, A *History of Drugs*, F. Hoffmann-La Roche & Co., Ltd, Basle, Switzerland, 1971, with permission).

Morphine, the most important alkaloid in opium, was obtained as a purified powder from opium in 1805 by Friedrich Wilhelm Sertürner (1783–1841), a German pharmacist's assistant [18]. He named it *morphium* after Morpheus, the Latin god of dreams, so named by Ovid using a Greek word. Later, the great French chemist and physicist Joseph-Louis Gay-Lussac (1778–1850), who was a strong supporter of Sertürner in his priority claim for the isolation of the substance over French pretenders, renamed the drug *morphine*, against the wishes of Sertürner [19]. The morphine molecule is a pentacyclic tertiary amine with five chiral centers **3** and the natural product is the levorotatory enantiomer.

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 **5**, 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 [10]. Heroin is a *semisynthetic* drug, i.e., a chemically modified derivative of a natural product, and retains the stereochemistry of mor-

phine. Heroin may have been the first synthetic unichiral drug introduced in clinical medicine.



Heroin was actively marketed to physicians by its manufacturer, as an advertisement from ca. 1900 shows (Fig. 1.2). The drug was touted as a "non-addicting" morphine analog that could safely replace morphine and thereby eliminate the latter's addiction problem [20]. This claim turned out to be tragically mistaken and today heroin is the most important abused opioid, with grave social, economic, and medical consequences. Another chiral drug, methadone, a totally synthetic opiate agonist, has been recruited to fight heroin addiction. Methadone was first synthesized, in the racemic form, in the 1940s and was later shown to have stereoselective opioid agonist properties, concentrated nearly exclusively in the (R)-(-) enantiomer **6** [21]. Methadone is used in the racemic form in the U.S. as an analgesic and in the treatment of opiate addiction, but in some other countries the pharmaceutical product is the unichiral *levo* form [22].

Perhaps the most fascinating old chiral drug, from a historical point of view, is quinine. Its earliest history is obscure, but it is known that by the early 1600s it was being used by South American natives in Peru, Ecuador, and neighboring regions



Fig. 1.2 Drug advertisement ca. 1900. (Reprinted from Roy Porter (Ed.), *Cambridge Illustrated History of Medicine*, Cambridge University Press, Cambridge, 1996, with permission).



as a crude preparation from the bark of the *cinchona* tree (Fig. 1.3) for the treatment of malaria. 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 [23] 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 regions of Africa and Asia, and even in Europe for centuries. 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 [24]. The quinine molecule contains four chiral carbon centers and the natural product is the levorotatory unichiral compound 7.

The name *cinchona* was coined by the Swedish botanist Linnaeus (Carl von Linné, 1707–1778) in honor of Doña Francisca Henriquez de Ribera, the fourth *Condesa* (Countess) of Chinchón and wife of the viceroy of Peru, a Spanish colony at the time [24, 25]. According to legend, in 1638 she was cured of malaria by the bark and, impressed with the cure, she took samples of cinchona to Spain, thereby



Fig. 1.3 One of the earliest illustrations of the cinchona tree, from Jonston's *Dendrographias*, published in 1662. (Reprinted from Mark Honigsbaum, *The Fever Trail*, Farrar, Straus and Giroux, New York, 2001, with permission).



launching the European career of the miracle remedy. However, as has been frequently pointed out, there are problems with Linnaeus' nomenclature. First, he misspelled *cinchona*, leaving out the first *h* in the countess' name; second, she died in South America before she could return to Spain [24, 25]. Be that as it may, cinchona has stuck in the official names of several species (e. g., *Cinchona officinalis* L and other species in the *Rubiaceae* family). As for *quinine*, this name is derived from *quina quina* ("bark of barks"), the Spanish spelling of a native Quechua name that was sometimes used for the cinchona tree in Peru, and was given by Pelletier and Caventou to their new substance [26].

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 was great, as the drug was in demand for the treatment of malaria not only in Europe but also in various parts of Africa and Asia, where European powers were engaged in establishing or strengthening their colonial control. Chemists in Europe were responding to the need with attempts to synthesize quinine in the laboratory. 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 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 [27] (Perkin's mauveine is a mixture of two compounds neither of which is chiral).

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 useful antimalarial agents, including the chiral drugs quinacrine 8, primaquine 9, and chloroquine 10. These compounds were introduced during the 20th century, in racemic form. Chloroquine (preparation patent issued 1939) was particularly useful inasmuch as it was cheap and effective, but more recently resistance by the malaria parasites to this drug has made it ineffective in many parts of the world where the disease is endemic [28]. Quinine remains a useful antimalarial agent in the treatment of chloroquine- and multidrug-resistant falciparum malaria today, but increasing resistance by the parasites may result in a reduction in the drug's importance in the future [29]. Malaria remains one of the great killers, with about 1–1.5 million victims dying of the disease every year, the majority of them African children [30].



The devastating disease scurvy is caused by insufficient amounts of L-ascorbic acid 11 (vitamin C) 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) (Fig. 1.4), 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 was nearly 50 years later, in 1795, that the British Admiralty finally took notice of these findings and instituted an appropriate diet on board Royal Navy ships to prevent scurvy [31]. Ascorbic acid was isolated by the Hungarian biochemist Albert Szent-Györgyi (1893–1986) from fruit juices in 1928 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 the structure and synthesis of ascorbic acid.



The above examples of old chiral drugs from natural sources are but a handful from a long list of many examples. Others include (some plant origins given in parentheses) tetrahydrocannabinol **12** (marihuana, hashish), digoxin (foxglove,



Fig. 1.4 James Lind, MD. From an engraving by I. Wright from a painting by Sir George Chalmers, Bart. (1783). The engraving forms the Frontispiece to the copy of Lind's *Essay on Diseases incidental to Europeans in Hot Climates* in the library of Haslar Hospital. The signature is from Lind's letter to Sir Alexander Dick. (Reprinted from C. P. Stewart and D. Guthrie (Eds.), *Lind's Treatise on Scurvy*, Edinburgh University Press, Edinburgh, 1953).

digitalis lanata Ehrh.), cocaine **13** (*erythroxylon*), cathinone (khat, *Catha edulis* Forsk.), nicotine **14** (tobacco, *Nicotiana tabacum*), atropine (deadly nightshade, *atropa belladonna* L.), reserpine (*Rauwolfia*), colchicine **15** (autumn crocus, meadow saffron), and emetine (ipecac), to name only a few. Each of these chiral compounds has an interesting history but these accounts are beyond our scope here. The chemical structures encompassed by just these relatively few chiral molecules are highly varied. Stereochemically, atropine is an interesting case: this racemic substance is believed not to occur naturally, but its levorotatory form, (*S*)-(–)-hyos-cyamine **16**, occurs in several *Solanaceae* plant species and is racemized to atropine during isolation [32, 33]. This facile racemization reaction is the result of the stereochemical lability of the chiral center due to the presence of the adjacent carbonyl group and the β -hydroxy group, in combination with its benzylic position.



The vast majority of chiral drugs present in the old remedies were unichiral: 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.

The "pre-science" era of pharmacotherapy based on crude natural remedies came to an end as the 19th century was drawing to a close. The dawn of the modern era of therapeutics did not mean, however, the end of the therapeutic use of natural compounds, chiral or achiral; only the science and technology became different. Beginning with the first decades of the 20th century, natural products were routinely purified from their sources and their chemical structures were elucidated. Chirality, when present, was now recognized.

1.4 Recognition of Chirality in Drugs

The earliest recognition of chirality in drugs was intimately linked to the discovery of molecular chirality. The relevant background work that led to the discovery was accomplished mainly in France during the first half of the 19th century [34]. *Hemihedrism* in crystals – those of quartz – was first reported by René-Just Haüy (1743–1822), a French priest and crystallographer, in 1801 [35]. Circularly polarized light (often referred to as plane-polarized light) was discovered in 1809 by Étienne Louis Malus (1775–1812), and the physicist François Arago (1786–1853) made the first observation of optical rotation by a substance when he studied the effects of quartz crystals on polarized light [34].

French physicist Jean-Baptiste Biot (1774-1862) discovered beginning in 1815 that certain organic compounds rotate polarized light in the noncrystalline state, e.g., in the liquid or solution state. Among these compounds were sucrose, turpentine, camphor, and tartaric acid [34]. Tartaric acid obtained from tartar deposits produced by the fermenting juice of grapes during the wine-making process was discovered by the Swedish pharmacist Carl Wilhelm Scheele (1742–1786) in 1769 [36], and Biot showed that the compound was dextrorotatory [37]. Biot understood that optical rotation by substances in the noncrystalline state was the result of some structural property of the molecules, and he referred to such compounds as substances moléculairement actives (molecularly active substances). This realization by Biot of a molecular-structural cause of optical rotation, coupled with his discovery in 1815 of the optical rotation of (+)-camphor 17, a therapeutic agent, may be considered the earliest scientific hint for chirality in drugs. Camphor, a carminative, rubefacient, and a mild expectorant, is stereochemically a rare example in the field of chiral natural products in that both enantiomers occur in nature. However, (+)-camphor was the only form known in the early 1800s when Biot undertook his studies; (-)-camphor was not discovered until 1853 [38].



A fuller appreciation of the existence of chiral drugs was achieved a few decades later by the celebrated French chemist (and later microbiologist) Louis Pasteur (1822–1895). Pasteur was familiar with the above-outlined work of Biot on optical rotation by organic compounds. In 1848 he found that the crystals of sodium ammonium tartrate (from dextro-tartaric acid) were hemihedral, i.e., there were small facets at alternate corners of the crystals [39]. He recognized that these facets rendered the crystals chiral (Pasteur used dissymmetric in the meaning of chiral - the latter term was coined by Lord Kelvin only in 1893 [40]). Pasteur then examined the sodium ammonium salt of another, related, acid. That acid had been obtained in 1820 - unexpectedly and on a single occasion - as a side-product during the manufacture of (+)-tartaric acid from tartar at a chemical plant in Thann, Alsace, France [41]. The mysterious new acid intrigued chemists. In 1826 Gay-Lussac obtained a sample for study and named it racemic acid, from racemus, Latin for cluster of grapes [42]. Racemic acid was found to be identical with (+)-tartaric acid, with the exception that - inexplicably at the time - it did not rotate polarized light, a fact first shown by Biot [43].

Pasteur obtained a sample of the new acid [41, 44] and found - to his initial dismay - that the crystals of sodium ammonium racemate, like those of the corresponding (dextrorotatory) tartrate, were hemihedral (he had predicted that the crystals of the optically inactive acid would not be hemihedral or chiral). To his surprise, however, he observed that there were two different crystals present in the salt of racemic acid. That is, in some of the crystals the hemihedral facets were inclined to the right and some to the left (as in quartz), and Pasteur recognized that the two crystals were related to each other as the two hands, i.e., they were enantiomorphous. Pasteur then manually separated the two kinds of crystals and found that they rotated polarized light in solution, the rotations by the two being equal in absolute value (within experimental error) but opposite in direction. The dextrorotatory salt thus obtained was identical in all respects to the corresponding salt of the known (+)-tartaric acid and could be converted to a free acid that was identical in all respects with (+)-tartaric acid, while the levorotatory salt gave an acid that was identical with the natural acid except that it rotated polarized light in the opposite direction. These results led Pasteur to the realization that its crystals were enantiomorphous and the molecules of the two substances in racemic acid must be chiral, due to some 3-dimensional feature of their molecular structure, and that they are mirror-image (i.e., enantiomeric) molecules [39]. This was the discovery of molecular chirality - the year was 1848 and Pasteur had not yet turned 26 years old. The discovery also opened the road toward an appreciation and development of drug chirality.

The first steps on that road were taken by Pasteur himself. In the early 1850s he went on to study many chiral compounds, among them quinine, quinidine 18, (an antiarrhythmic drug and a diastereoisomer of quinine also obtained from cinchona), etc. He recognized that these molecules were chiral and that the substances isolated from their natural sources were unichiral, and he measured their optical rotation and described their crystal habit [45]. Quinine was already well-known as an antimalarial agent at the time (see above) and we may therefore consider Pasteur's description of this drug as chiral to have been the first clear recognition of molecular chirality in a therapeutic agent. Later, in a lecture in 1860 on the dissymmetry of natural products, Pasteur stated the essence of the matter: ... morphine, codéine, quinine, strychnine, brucine, ...Tous ces principes immédiats sont moléculairement dissymétriques." (... morphine, codeine, quinine, strychnine, brucine, ... All these natural compounds have molecular dissymmetry) [46]. Clearly, Pasteur was the first to appreciate that certain drug molecules are chiral.



From the chirality standpoint the next fundamental development occurred in 1874, when the tetrahedral carbon atom was proposed as a basis for molecular chirality by the Dutch and French chemists Jacobus Henricus van't Hoff (1852–1911) [47, 48] and Joseph Achille LeBel (1847–1930) [49], respectively, independently and almost simultaneously. The discovery of the "asymmetric carbon atom" (van't Hoff's terminology) finally provided the explanation for the existence of "optical isomers" and for the chiral nature of the molecules of optically active substances, including many drugs. In his original 1874 pamphlet proposing the tetrahedron [47] van't Hoff listed camphor as a chiral molecule, but the structure he gave (**19**) was incorrect.



Advances in organic chemistry during the second half of the 19th century began the era of the elucidation of the structures of organic molecules, including many chiral molecules. By the early 1880s the 2-dimensional structures (i. e., the connectivity of the atoms) of many relatively simple organic compounds were elucidated, but the structures of more complex molecules were not known. For example, the English edition of *Adolph Strecker's Short Text-Book of Organic Chemistry* (1882), written by Johannes Wislicenus (1835–1902), a leading German chemist of the time, included many naturally occurring chiral drugs, e.g., camphor, codeine, morphine, quinidine, quinine, etc., and optical rotation data was provided for many of them, but their chemical structures were not addressed. Similarly, the second edition of *Watts' Dictionary of Chemistry*, a standard compendium published during the period 1892–1899, had no, or incorrect, structures for the complex drugs mentioned above.

By the end of the 19th century, despite limitations in the elucidation of complex organic structures, many chiral pharmacologically active compounds became available, often in both enantiomeric forms. This in turn led to studies comparing the enantiomers for their pharmacological actions and biological fate.

1.5

Enantioselectivity in Drug Action and Drug Metabolism: The Beginnings

The first observation of biological enantioselectivity was made by Pasteur himself. He found, in 1858, that when solutions of racemic ammonium tartrate were fortified with "organic matter" (i.e., a source of microorganisms) and allowed to stand, the solution "fermented" and (+)-tartaric acid was consumed rapidly while (–)-tartaric acid was left behind unreacted. Eventually the (–)-enantiomer was also metabolized, but considerably more slowly than (+)-tartrate [50]. In later experiments Pasteur showed that the common mold *Penicillium glaucum* metabolized (+)-tartaric acid with high enantioselectivity [51]. He correctly theorized that the enantioselective destruction of tartaric acid by microorganisms involves selective interaction of the tartrate enantiomers with a key chiral molecule within the microorganism [50, 51].

Towards the end of the 19th century the role of chirality in biological activity began to receive serious attention. Two lines of investigation were pursued: one focused on the metabolic fate of chiral compounds while the other examined their pharmacological activity. The first report of enantioselectivity in what may be considered a pharmacological effect appeared in 1886, when (+)-asparagine was found to have a sweet taste while (–)-asparagine was without taste [52]. Pasteur, aware of the finding, interpreted the results as an indication of the presence of a unichiral compound in the nervous system of taste, suggesting that the interactions of the asparagine enantiomers with the chiral biological mediator were different [53]. During the period from the mid-1880s to the mid-1920s many studies comparing the enantiomers of pharmacologically active compounds were carried out, and many examples of enantioselective pharmacological effects were observed. As an example, (–)-hyoscyamine **16** was found to be ca. 12–20 times more potent than the *dextro* enantiomer in a variety of pharmacological effects, e.g., mydriasis in the cat, salivary secretion in the dog, and at cardiac myoneural junctions. Interestingly, (+)-hyoscyamine was the more potent enantiomer in CNS-excitatory effects [54].

By the 1890s stereoselective action by enzymes on substrates was known, in large measure as a result of the monumental work of the great German chemist Emil Fischer (1852–1919) on sugars which spanned the period 1884–1907. Fischer first demonstrated that microbial fermentation of sugars (e.g., by beer yeast) displayed considerable enantioselectivity. Later Fischer extended these studies to the action of enzymes isolated from the microorganisms, and, here too, profound enantioselectivity was found in the reaction of sugars. From his structural and stereochemical studies of sugars as enzyme substrates Fischer concluded that overall shape and stereochemical configuration strongly influence the suitability of a molecule to serve as substrate for an enzyme. He condensed these spatial requirements in the statement that for an enzyme to act on a substrate the two must fit like a lock and its key [55].

It was against this background that a variety of *in vitro* investigations of enantioselectivity in the metabolism of a variety of chiral compounds were undertaken in the late 1800s and early 1900s. Enantioselective enzymatic reactions were shown *in vitro* for many physiological compounds, e.g., amino acids, peptides, lactic acid, etc., but some foreign compounds were also studied. For example, it was found that racemic β -(α -naphthyl)alanine **20** was enantioselectively metabolized by bacteria, the *levo* enantiomer being consumed while the *dextro* enantioform was untouched [56]. A complex picture of enzymatic stereoselectivity emerged from these studies: depending on the substrates and enzymes, in some cases no enantioselectivity was found while in others one of the enantioselectivity changed for the same substrate, depending on the enzyme [57].



Many in *vivo* studies of enantioselective metabolism were also carried out in the same period. For example, when (\pm) -camphor was fed to dogs or rabbits more of the *levo* enantiomer was converted to a glucuronyl conjugate than of the *dextro* enantiomer [58]. When (\pm) -malic acid was injected subcutaneously into the rabbit larger amounts of (+)-malate appeared in the urine, indicating that (-)-malate (the naturally occurring form) was more extensively metabolized [59].

In 1926 Arthur Robertson Cushny (1866–1926) (Fig. 1.5), a Scottish pharmacologist, reviewed the studies of enantioselective pharmacology and metabolism pub-



Fig. 1.5 Dr. Arthur Robertson Cushny. (Reprinted from V. C. Vaughan, *A doctor's memories*, The Bobbs-Merrill Company, Indianapolis, 1926).

lished during the previous ca. 40 years [60]. The review, which was the first extensive, detailed, and critical discussion of enantioselectivity in pharmacology, reveals a great deal of insight into the nature of chirality and its biological implications. Cushny also made important experimental contributions to the field [60] and was a true pioneer of chirality in pharmacology.

All in all, it is clear that early in the 20th century it was known that drug action and metabolism can be enantioselective. However, this knowledge remained largely in the academic halls of pharmacology, medicinal chemistry, and biochemistry and its broader implications for the creation of safer and more effective drugs were largely ignored until the last 20 years of the century.

1.6

Drug Chirality in the 20th Century

As described above, by the beginning of the 20th century examination of the role of chirality in drug action and disposition had begun and enantioselectivity was found in many cases. Such studies continued at an accelerated rate during the rest of the century. In 1933 Easson and Stedman proposed a fundamental model as the basis for enantioselective drug–receptor interactions [61]. This model was deduced from studies of the pressor effects of the enantiomers of epinephrine which showed a 300:1 enantioselectivity, the natural (R)-(–) form being the more potent enantiomer **21**. It was concluded that three groups in the molecule – the amino group, the aliphatic hydroxyl group and the electron-rich aromatic ring – interact with three complementary sites on the (chiral) receptor, and it was argued from the 3-dimensional geometry of contact between two chiral entities (the drug and the receptor) that if all three groups of one enantiomer will not be able to interact fully or in the same manner with the same three bonding sites on the receptor.

tor. Thus, the binding of the two drug enantiomers to the receptor can be significantly different, which in turn may produce different biological effects by the enantiomers. The 3-point-interaction model, originally proposed for a specific effect of epinephrine, was later broadened to explain biological enantioselectivity of chiral drugs in general [62], be it in drug–receptor interactions, enzyme–substrate interactions, protein binding, etc. Moreover, the 3-point-interaction model of enantioselectivity has also been used in chromatography to explain enantioselective retention arising from interactions of the chiral analyte molecules with the molecules of the chiral stationary phase or other chiral selectors [63].



With the advances in organic chemistry in the early decades of the century the more complex drugs began to yield their chemical structures. For example, the structure of morphine was proposed in 1923 [64]; the drug was synthesized in 1952 [65], and its absolute configuration was determined in 1955 [66]. (+)-Morphine was synthesized in 1960 and was shown to differ significantly from the natural (–)-morphine in that it lacks analgesic activity. (+)-Morphine does possess antitussive activity, albeit to a lesser extent than (–)-morphine [67].

The correct connectivity of the atoms of the quinine molecule was determined early in the 20th century by Rabe [68] but without establishing the stereochemistry of the molecule. Attempts were made by several groups over subsequent decades to synthesize quinine stereoselectively, but success was not obtained until 2001 [69], 181 years after the compound was first isolated.

It should be pointed out here that the firm establishment of the *absolute* configuration of chiral drugs, as of other chiral molecules, by an experimental method had to await the famous experiment of 1951 in which Bijvoet et al. determined the absolute configuration of sodium rubidium tartrate using the technique of anomalous X-ray scattering [70]. This milestone in stereochemistry opened the door to the elucidation of the absolute configuration of thousands of compounds, including many drugs.

Chirality continued to occupy pharmacologists and chemists during the remainder of the century. Enantioselectivity in the effects or disposition of chiral drugs was found in a large number of cases, for a large variety of pharmacological effects and chemical structures. To mention a few examples, in 1940 significant biological differences between the enantiomers of sex hormones, e.g., those of the steroid equilenin **22**, were reported [71]; the β -adrenergic-antagonist activity of propranolol, the first commercially successful beta blocker, was determined to be lopsidedly in the (*S*)-(–) enantiomer **23**, and similar selectivity was found in several other, related, β -adrenergic antagonists [72]. Examples of enantioselective toxicity were also found, e.g., levodopa (L-3,4-dihydroxyphenylalanine **24**). 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 unichiral, L, form [73]. By the 1970s a large body of information had accumulated on the role of chirality in drug action and metabolism, and many reviews and monographs on the subject appeared during the last ca. 30 years of the century, for example [74–79]. In 1973 a seminal review of stereoselectivity in drug biotransformations and metabolism was published by Jenner and Testa [80].



Modern pharmacotherapy came of age during the 20th century. Many new pharmacologically active natural products were isolated and identified, thousands of new compounds (many of them chiral) were synthesized and examined for pharmacological effects and therapeutic potential, and a large number of new drugs were introduced into the armamentarium of the physician. As mentioned above, by 1987 ca. 55% of all clinically used drugs were based on chiral molecules [2]. Many of the new chiral drugs introduced were natural products or semisynthetic derivatives thereof and, as Ariens and Wuis pointed out, a vast majority, ca. 98%, of such drugs were introduced in unichiral form [2]. Atropine was one of the few exceptions. As the racemized derivative of the naturally occurring (–)-hyoscyamine (see above), atropine may be considered a semisynthetic agent and may have been the first synthetic racemic drug introduced into medical practice. The drug was first isolated in 1833, its pharmacological properties studied in the 1880s, and the compound was synthesized in 1901 [81]. A patent for the preparation of atropine sulfate was issued in 1912.

With time, entirely synthetic chiral drugs began to form a major segment of the new therapeutic agents. This trend began slowly early in the century, but by the 1950s the number of such drugs was increasing rapidly. The vast majority of synthetic chiral drugs introduced by 1987, ca. 88%, were racemic, and by the late 1980s roughly a quarter of the drugs on the market were chiral and racemic [1, 2]. Among the earliest entirely synthetic racemic drugs were several anticonvulsant or sedative barbituric-acid derivatives, e.g., pentobarbital **25**, for which a preparation patent was issued in 1916. In this context it is also of interest that the first report of the synthesis of the enantiomers of a barbituric acid and a comparison of their efficacy and toxicity appeared as early as 1928 [82].

It is also noteworthy that some of the chiral drugs introduced as stereochemical mixtures were more complex than the simple racemate. For example, some new agents were marketed as a mixture of two or more racemic mixtures, e.g., labeta-lol **26** (2 racemates, preparation patent 1971) [83], and cyclothiazide **27** (4 race-



mates, preparation patent 1966) [84]. In such cases it was sometimes claimed that all or most of the stereoisomers contributed therapeutically useful activity, but it is difficult to avoid the conclusion that synthetic considerations and their cost implications weighed heavily in the decision to market the complex mixture. A few other chiral drugs were mixtures of epimers, resulting either from the stereochemical instability of a chiral center within the molecule, e.g., carbenicillin **28** (preparation patent 1964) or from nonstereoselective synthesis, e.g., the prodrug cefpodoxime proxetil (preparation patent 1982).



Overall, then, a vast majority of synthetic chiral drugs were introduced during the 20th century in racemic (or, in a few cases, in other stereoisomeric mixture) form, as discussed above. It is relevant in this regard that the clinical use of some racemic drugs was stopped or severely curtailed due to toxicity that became evident only after introduction of the drug on the market, e.g., the antiarrhythmic agent tocainide **29** [85] and the analgesic and anti-inflammatory drug benoxaprofen **30** [86]. One may wonder whether in such cases the adverse effects in question may be enantioselective, i.e., whether a unichiral version (that excludes the more toxic enantiomer) would have been a safer drug.



It should be noted, however, that despite the general preference for the marketing of synthetic chiral therapeutic agents in racemic form, a few synthetic chiral drugs *were* introduced in a unichiral form. Such exceptions included the abovementioned levodopa and also p-penicillamine **31** [78], (–)-timolol **32** [87], methyldopa **33** [88], etc, and it is clear that in most such cases the choice of developing a unichiral form was dictated by overt serious toxicity present predominantly in the other enantiomer.



From the above considerations of new-drug development in the 20th century a clear conclusion can be drawn: during most of the century pharmaceutical firms did not make an effort to study the role of chirality in new-drug candidates and did not have a great deal of interest in developing unichiral drugs if nature did not provide them. This lack of interest in chirality from the industry may have been the result of a lack of interest in chirality from governmental drug-regulatory agencies. For example, until 1987 the FDA did not explicitly require the inclusion of information on the enantiomer composition of chiral substances in new-drug applications [89].

A broad and serious examination of the role of chirality in new-drug development only began during the 1980s. The driving force behind this change in attitudes must be ascribed to the advent of enantioselective analytical methods capable of selectively detecting and measuring the individual enantiomers in the presence of each other [90]; to the development of powerful new methods for the synthesis of unichiral compounds [91], and to preparative chromatographic methods for the separation of drug enantiomers on a useful scale for pharmacological testing [92].

The new climate in chiral drugs produced discussions of the merits of the development of unichiral agents vs. racemic mixtures as new drugs, e.g., [78, 93, 94]. A great deal of evidence accumulated in favor of unichiral drugs. The unichiral drug is a single agent instead of a mixture of two distinct drugs, which simplifies the interpretation of the basic pharmacology, therapeutic and toxic effects, pharmacokinetic properties, and the relationship of plasma concentrations to effects. Other advantages may include reduced dosage, reduced drug interactions, and reduced toxicity. This, however, is a complex matter and each drug must be judged on its own merits [78, 93–95]; indeed, the preference for unichiral drugs is not absolute, and in several cases a unichiral form proved to be less safe than the racemic (or some other) mixture of stereoisomers, e.g., fluoxetine **34** [96], labetalol **26** [97], and sotalol **35** [78]. The explanation for this phenomenon may be a direct pharmacodynamic or pharmacokinetic competition/interaction between the stereoisomers which results in the prevention by one stereoisomer of toxicity by another (as is likely to be the case for labetalol), or a specific protective effect provided by one of the enantiomers in the racemic mixture (as in the case of sotalol) [98]. About 25 years ago a novel concept in this regard was introduced by Tobert et al. on the basis of their studies of the diuretic and uricosuric agent indacrinone **36**: the *non-racemic* mixture of the enantiomers as an optimized drug. The optimum therapeutic effects for indacrinone were obtained with the 4:1 *S/R* mixture of the enantiomers [99]. The broad applicability of this concept remains to be determined.



We end our tour of the history of chiral drugs with the year 1992, when the FDA issued its guidelines governing the development of new chiral drugs [100]. In roughly the same period other regulatory bodies around the world, e.g., the agencies of the European Union, Canada, Japan, Australia, etc., issued similar guidelines (although the various agencies differ somewhat in the level and detail of some of the requirements) [101]. While the new regulations do not ban the introduction of new racemic drugs, their overall effect is in fact the near-total disappearance of racemic substances as new drugs. Henceforth, the overwhelming majority of new chiral drugs will be unichiral. Such drugs are developed as new chemical entities or are obtained, less frequently, via a *chiral switch*, in which a single-enantiomer from an existing racemic drug is developed as a new drug [98]. We have come full circle: After nearly 5000 years of single-enantiomer chiral therapeutics, followed by about 100 years of a strong trend towards racemic formulation, unichiral drugs are again the order of the day.

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References

- M. Simonyi, Med. Res. Rev. 1984, 4, 359– 413.
- **2** E. J. Ariens, E. W. Wuis, *Clin. Pharmacol. Ther.* **1987**, *42*, 361–363.
- 3 E. L. Eliel, S. H. Wilen, L. N. Mander, Stereochemistry of Organic Compounds, Wiley-Interscience, New York, 1994, p. 1194.
- 4 K. Mislow, Topics Stereochem. 1999, 22, 1.
- 5 J. Gal, Enantiomer, 1998, 3, 263-273.
- 6 G. Thomas, Medicinal Chemistry: An Introduction, John Wiley & Sons, Ltd, UK, 2000, p. 3.
- 7 A. Burger, Introduction: History and Economics of Medicinal Chemistry, in M. E. Wolff (Ed.), *Burger's Medicinal Chemistry*, Part I , 4th edn., John Wiley & Sons, New York, **1980**, pp. 7–22.
- 8 A. Burger, Drugs and People: Medications, Their History and Origins, and the Way They Act, University Press of Virginia, USA, 1986, p. 4.
- **9** See Ref. 8, pp. 4–5
- 10 See Ref. 7, p. 8.
- 11 K. K. Chen, C. F. Schmidt, Medicine (Baltimore, MD) 1930, 9, 1–117.
- 12 B. B. Hoffman, Catecholamines, Sympathomimetic Drugs, and Adrenergic Receptor Antagonists, in J. G. Hardman, L. E. Limbird, A. G. Gilman (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edn., McGraw-Hill, New York, 2001, p. 237.
- 13 G. D. Newton, W. S. Pray, N. G. Popovich, J. Am. Pharm. Assoc. 2004, 44, 211–225.
- 14 D. M. Perrine, *The Chemistry of Mind-Altering Drugs – History, Pharmacology, and Cultural Context, American Chemi*cal Society, Washington DC, 1996, pp. 44–45.
- 15 W. O. Foye, Medicinals of Plant Origins: Historical Aspects, in W. O. Foye, T. L. Lemke, D. A. Williams (Eds.), *Principles*

of Medicinal Chemistry, 4th edn., Lippincott, Williams and Wilkins, USA, **1995**, p. 8.

- 16 See Ref. 8, p. 15.
- 17 See Ref. 7, p. 3.
- **18** F. W. A. Sertürner, J. Pharm. **1805**, *13*, 229–243.
- 19 F. W. A. Sertürner, Ann. Phys. 1817, 57, 183–202.
- 20 M. R. Johnson, Analgetics, in M. E. Wolff (Ed.), *Burger's Medicinal Chemistry*, Part III, 4th edn., Wiley-Interscience, New York, 1981, p. 707.
- 21 See Ref. 20, pp. 708–709, 735.
- 22 C. P. Eap, T. Finkbeiner, M. Gastpar, N. Scherbaum, K. Powell, P. Baumann, *Eur. J. Clin. Pharmacol.* 1996, *50*, 385–89.
- 23 M. Honigsbaum, The Fever Trail. In Search of the Cure for Malaria, Farrar, Straus, and Giroux, USA, 2001, pp. 24–25.
- 24 J. Pelletier, J.-B. Caventou, Ann. Chim. Phys. 1820, 15.
- 25 See Ref. 23, pp. ix-x.
- **26** See Ref. 23, pp. x, xiii.
- S. Garfield, Mauve: How One Man Invented a Color that Changed the World,
 W. W. Norton & Co., USA, 2000.
- 28 J. W. Tracy, L. T. Webster, Jr., Chemotherapy of Parasitic Infections, in J. G. Hardman, L. E. Limbird, A. G. Gilman (Eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Edition, McGraw-Hill, New York, 2001, p. 1092.
- 29 See Ref. 28, p. 1087.
- 30 See Ref. 28, p. 1069
- 31 M. Weatherall, Drug Treatment and the Rise of Pharmacology, in R. Porter (Ed.), *The Cambridge Illustrated History of Medicine*, Cambridge University Press, Cambridge, 1996, p. 256.

- 32 J. H. Brown, P. Taylor, Muscarinic Receptor Antagonists, in J. G. Hardman, L. E. Limbird, A. G. Gilman (Eds.), *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th edn., McGraw-Hill, New York, 2001, p. 164.
- 33 V. S. Venturella, Natural Products, in A. R. Gennaro (Ed.), *Remingtons Pharmaceutical Sciences*, 17th edn., Mack Publishing Company, USA, 1985, p. 418.
- 34 E. L. Eliel, S. H. Wilen, L. N. Mander, Stereochemistry of Organic Compounds, Wiley-Interscience, USA, 1994, pp. 2–4.
- 35 R.-J. Haüy, Traité de Minéralogie, Conseil des Mines, France, 1801.
- 36 H. Kopp, Geschichte Chem. 1847, 4, 349.
- **37** J.-B. Biot, Bull. Soc. Philomatique **1815**, 190–192.
- 38 J. Chautard, Compt. Rend. Acad. Sci. 1853, 37, 166–167.
- **39** L. Pasteur, Compt. Rend. Acad. Sci. 1848, 34, 535–538.
- 40 W.T. Kelvin, J. Oxford Univ. Jr. Sci. Club 1894, No. 18, 25.
- 41 L. Pasteur, Ann. Chim. Phys. 1850, 3^e sér. 28, 56–99.
- 42 J. L. Gay-Lussac, Schweigger's J. 1826, 48, 381.
- 43 J.-B. Biot, Ann. Chim. Phys. 1838, 69, 22.
- 44 L. Pasteur, Compt. Rend. Acad. Sci. 1853, 36, 19–26.
- 45 L. Pasteur, Compt. Rend. Acad. Sci. 1853, 37, 110–114.
- 46 L. Pasteur, Recherches sur la Dissymétrie Moléculaire des Produits Organiques Naturels, in *Leçons de chimie professées en* 1860 par MM. Pasteur, Cahours, Wurtz, Berthelot, Sainte-Claire Deville, Barral et Dumas, Hachette et C^{ie}, France, 1860, in-88, pp. 1–48.
- 47 J. H. van,t Hoff, Voorstel tot Uitbreiding der tegenwoordig in de scheikunde gebruikte Structuur-Formules in de ruimte: benevens een daarmeê samenhagende opmerkung omtrent het verband tusschen optisch actief Vermogen en Chemische Constitutie von Organische Verbindingen, Utrecht, Netherlands, 1874.
- **48** J. H. van,t Hoff, *La chimie dans l'espace*, Bazendijk, Netherlands, **1875**.
- 49 J. A. LeBel, Bull. Soc. Chim. 1874, 22, 337–347.

- **50** L. Pasteur, Compt. Rend. Acad. Sci. 1858, 46, 615–18.
- 51 L. Pasteur, Compt. Rend. Acad. Sci. 1860, 51, 298–99.
- 52 A. R.Cushny, Biological Relations of Optically Isomeric Substances, The Williams and Wilkins Company, USA, 1926, p. 37.
- 53 L. Pasteur Compt. Rend. Acad. Sci. 1886, 103, 138.
- 54 A. R. Cushny, J. Pharmacol. Exper. Ther. 1920, 15, 105–27.
- 55 P. J. Ramberg, Chemical Structure, Spatial Arrangement, The Early History of Stereochemistry, 1874–1914, Ashgate Publishing Limited, UK, 2003, pp. 268–272.
- **56** T. Sasaki and J. Kinose, *Biochem. Z.* **1921**, *121*, 171–4.
- 57 See Ref. 52, pp. 18-29.
- 58 See Ref. 52, p. 34.
- 59 N. Tomita, *Biochem. Z.*, 1921, 123, 231–4.60 See Ref. 52.
- 61 L. H. Easson, E. Stedman, *Biochem. J.*
- **1933**, *27*, 1257–66.
- 62 E. J. Ariëns, Racemates an impediment in the use of drugs and agrochemicals, in A. M. Krstulovic (Ed.), *Chiral Separations by HPLC*, Ellis Horwood Limited, UK, 1989, pp. 31–68.
- 63 L. R. Snyder, J. J. Kirkland, J. L. Glajch, J. Kern, K. Kirkland, Chiral Separations", in L. R. Snyder, J. J. Kirkland, J. L. Glajch (Eds.), *Practical HPLC Method Development*, Wiley-Interscience, USA, 1997, p. 544.
- 64 J. M. Gulland, R. Robinson, J. Chem. Soc., 1923, 123, 980–98.
- 65 M. Gates, G. Tschudi, J. Am. Chem. Soc., 1952, 74, 1109–10.
- 66 J. Kalvoda, P. Buchschacher, O. Jeger, *Helv. Chim. Acta*, 1955, 38, 1847–56.
- 67 D. Miller, Antitussives, in M. E. Wolff, Burger's Medicinal Chemistry, Part III, 4th edn., Wiley-Interscience, USA, 1981, p. 763.
- **68** P. Rabe, K. Kindler, *Ber*ichte 1918, 51, 466–467.
- 69 G. Stork, D. Niu, A. Fujimoto, E. R. Koft, J. M. Balkovec, J. R. Tata, G. R. Dake, J. Am. Chem. Soc, 2001, 123, 3239–3242.
- **70** J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature*, **1951**, *168*, 271–272.

- 26 1 Chiral Drugs from a Historical Point of View
 - 71 W. E. Bachmann, W. Cole, A. L. Wilds, J. Am. Chem. Soc., 1940, 62, 824–839.
 - 72 B. G. Main, Beta-Adrenergic Blockers: Properties of the Enantiomers, in M. Simonyi (Ed.), Problems and Wonders of Chiral Molecules, Académiai Kiadó, Hungary, 1990, pp. 329–343.
 - 73 G. C. Cotzias, P. S. Papavasiliou,
 R. Gellene, *New Engl. J. Med.*, 1969, 280, 337–345.
 - 74 P. S. Portoghese, Ann. Rev. Pharmacol. 1970, 10, 51–76.
 - 75 B. V. Rama Sastry, Ann. Rev. Pharmacol. 1973, 13, 253–267.
 - 76 E. J. Ariens, Med. Res. Rev., 1986, 6, 451– 466.
 - 77 I. W. Wainer (Ed.), Drug Stereochemistry: Analytical Methods and Pharmacology, 2nd edn., Marcel Dekker, New York, 1993.
 - **78** A. J. Hutt, S. C. Tan, *Drugs*, **1996**, *52*, Suppl. 5, 1–12.
 - 79 M. Eichelbaum, A. S. Gross, Adv. Drug. Res. 1996, 28, 1–64.
 - 80 P. Jenner, B. Testa, Drug Metab. Rev. 1973, 2, 117–184.
 - 81 A. Burger, Introduction: History and Economics of Medicinal Chemistry, in M. E. Wolff (Ed.), *Burger's Medicinal Chemistry*, Part I, 4th edn., John Wiley & Sons, New York, 1980, p. 7.
 - 82 C.-m. Hsueh, C. S. Marvel, J. Am. Chem. Soc. 1928, 50, 855–859.
 - 83 J. R. Powell, J. J. Ambre, I. R. Tsuen, The Efficacy and Toxicity of Drug Stereoisomers, in Ref. 77, pp. 249–250.
 - 84 E. Nusser, A. Banerjee, J. Gal, *Chirality* 1991, 3, 2–13.
 - 85 K. Volosin, R. M. Greenberg, A. J. Greenspon, Am. Heart J. 1985, 109, 1392–1393.
 - 86 J. Abraham, Sci. Technol. Hum. Val., 1994, 19, 493–522.
 - 87 J. J. Baldwin , W. B. Abrams, Stereochemically Pure Drugs, in Ref. 77, pp. 317– 318.

- 88 L. Gillespie, J. A. Oates, J. R. Crout, A. Sjoerdsma, *Circulation*, 1962, 25, 281– 291.
- 89 W. H. De Camp, Chirality 1989, 1, 2-6.
- **90** A. M. Krstulovic (Ed.), *Chiral Separations by HPLC*, Ellis Horwood Limited, UK, **1989**.
- 91 L. N. Mander, Stereoselective Synthesis, in E. L. Eliel, S. H. Wilen, L. N. Mander (Eds.), *Stereochemistry of Organic Compounds*, Wiley-Interscience, USA, 1994, pp. 835–990.
- 92 E. Francotte, Preparation of Drug Enantiomers by Chromatographic Resolution on Chiral Stationary Phases, in H. Y. Aboul-Enein, I. W. Wainer (Eds.), *The Impact of Stereochemistry on Drug Development and Use*, Wiley-Intescience, USA 1997, pp. 633–683.
- **93** B. Testa, W. F. Trager, *Chirality* **1990**, *2*, 129–133.
- 94 I. Szelenyi, G. Geisslinger, E. Polymeropoulos, W. Paul, M. Herbst, K. Brune, Drug News Perspect. 1998, 11, 139–160.
- **95** T. A. Baillie, K. M. Schultz, Stereochemistry in the Drug Development Process: Role of Chirality as a Determinant of Drug Action, Metabolism, and Toxicity in Ref. 92, pp. 21–43.
- 96 A. Thayer, Chem. Eng. News 2000, 78, 8.
- 97 E Riva, T Mennini, R Latini, Br. J. Pharmacol. 1991, 104, 823–828.
- **98** J. Gal, CNS Spectrums, **2002**, 7 (Suppl. 3), 45–54.
- 99 J. A. Tobert, V. J. Cirillo, G. Hitzenberger, I. James, J. Pryor, T. Cook, A. Buntinx, I. B. Holmes, P. M. Lutterbeck, *Clin. Pharmacol. Ther.* 1981, 29, 344–350.
- 100 Anonymous, Fed. Reg., May 27, 1992, 5(102), 22249.
- 101 S. Laganière, Current Regulatory Guidelines of Stereoisomeric Drugs: North American, European, and Japanese Point of View, in Ref. 92, pp. 545–564.